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MODERN VIEWPOINTS IN THE TREATMENT OF THYREOTOXICOSIS.[1]

By HUGH R. G. POATE,
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Iodine Therapy.

WITH the advent of iodine treatment as a routine measure in the pre-operative preparation of patients with thyreotoxicosis great advances were made in the surgical treatment of this complaint and an average operative mortality rate of some 16% to 20% was brought down to about 5%. Iodine, however, was subjected to abuse, chiefly by those practitioners who did not take the trouble to acquaint themselves with the normal needs of the body for this mineral or with its effects in abnormal states of the thyreoid gland. As a result the surgeon found that technical difficulties at operation were frequently increased, owing to the hyperiodized condition of the gland resulting from prolonged treatment and overdosage with the drug.

It may be advisable to recapitulate some of the salient facts with regard to iodine.

The normal thyreoid gland contains about 25·0 milligrammes of iodine, chiefly in the form of thyroxin (which is 60% iodine), and the circulating blood contains 10 microgrammes of iodine, partly in combination and partly in its inorganic form. The normal needs of the body are met with only 0·3 to 0·5 milligramme per week—a fact to bear in mind when one is ordering iodine for patients. Lugol's solution contains 9·0 milligrammes of iodine in three minims, and if it is given three times a day this dosage supplies in twenty-four hours more than the normal content of the thyreoid gland; if the dosage is continued for one week it supplies some 600 times more than the normal body requirement. The thyreoid gland in thyreotoxicosis is low in iodine content and seizes on any available inorganic iodine, so that it soon builds up its full storage capacity. This is the reason for the good clinical response in ten to fourteen days, the time when operation is best undertaken. Beyond this period the gland becomes choked, iodine thyreoiditis and perithyreoiditis develop and thyreotoxic manifestations recur.

The role of iodine must be understood if thiouracil is to be used in preparing thyreotoxic patients for operation. All observers report a definite lag in the response to thiouracil if patients have had previous iodine therapy, and its correct place as a pre-operative measure will be dealt with later.

Anæsthesia.

One of the most important developments in the surgery of toxic goitre has been the recognition of anæsthesia as a specialized branch of scientific medicine. Owing to the lack of understanding and the poor methods of general anæsthesia in vogue, many surgeons developed the technique of thyreoidectomy under local anæsthesia as being easier for both patient and surgeon. However, with the development of machine anæsthesia an increased knowledge of how the various anæsthetic agents act and the realization of what anoxia means have brought a great change over thyreoid surgery. The anæsthetist has now become an active member of the surgical team in both pre-operative and post-operative treatment, as well as in the administration of the anæsthetic. In fact, he plays a major part in ensuring for the patient a calm convalescence, free from those chest complications which used to cause embarrassment in so many cases.

The role of the anæsthetist has been greatly modified with the advent of thiouracil, as patients adequately prepared for operation with this drug do not require the heavy premedication that used to be necessary, and the

[1] Read at a meeting of the Royal Australasian College of Surgeons on June 11, 1946, at Sydney.

anæsthesia can be maintained at a steady level with lower concentrations of the anæsthetic agents; in fact, the period spent in the operating theatre is so tranquil that there is no strain on either patient or anæsthetist. In cases of toxic adenomatous goitre added anæsthetic difficulties may be caused by varying degrees of obstruction due to compression of the trachea, either lateral or antero-posterior, according to the position of the substernal or intrathoracic adenomatous masses. Carcinoma of the thyreoid may also cause difficulty in induction as well as in maintenance of the level of anæsthesia.

It should be the duty of the anæsthetist to examine the larynx before operation, especially (*a*) when a large tumour is present, (*b*) when malignant disease is suspected and (*c*) when any previous operation has been performed on the gland, as it is common to find a paralysed vocal cord even apart from surgical trauma.

The vital importance of avoiding any degree of anoxæmia has been appreciated and the technique developed to prevent such a condition has been one of the greatest safety factors in the surgical treatment of thyreotoxicosis in recent years and has played a large part in reducing the operative mortality rate from some 4·0% to 0·5%, a figure that we have achieved in the last eight or ten years. The adoption of the closed-circuit, carbon-dioxide absorption technique allowing the administration of a high percentage of oxygen during anæsthesia, along with the immediate post-operative aspiration of all mucus from trachea and bronchi, has brought about an easy recovery period and an avoidance of complications pleasing to patient, nurses and the surgeon; this is a state of affairs for which the anæsthetist is wholly responsible, and to him all credit should be given.

The quick, easy induction of anæsthesia that is so desirable is achieved by correctly assessing the patient's condition and choosing the form of premedication most likely to attain this object. Similarly, a quick and effortless intubation can be carried out by spraying the back of the throat and larynx with 2% "Decicain" solution as soon as the patient is lightly anæsthetized, and by following this procedure a few minutes later by the passage of a Magill's tube under direct vision rather than by attempting a "blind" introduction which demands a deep level of anæsthesia if laryngeal spasm is to be avoided. The immediate post-operative examination of the larynx is a routine procedure, not only for the aspiration of all mucus, but so that the condition of the vocal cords and of the trachea itself can be observed, as in those cases in which pressure has brought about absorption of the cartilagenous rings of the trachea, the walls may collapse and cause a most embarrassing obstruction to respiration—a state of affairs which can be avoided by leaving a Magill's tube in place until the patient recovers consciousness. If there is any doubt as to the mobility of the cords, the patient should be watched carefully for ten or fifteen minutes before being returned to bed, and if the doubt persists a Magill's tube should be inserted and left until consciousness is regained.

The anæsthetist also follows the patient to the bed and is responsible for the correct administration of oxygen should this be required, and upon him may rest the decision as to whether a Magill's tube should be reinserted (by the nasal route) or tracheotomy performed. Also he is in a position to decide whether any intravenous therapy should be instituted.

The Thio Compounds.

The advent of the thio compounds has perhaps brought about the greatest change in the treatment of thyreotoxicosis that has eventuated in the history of this complaint. Although it is only just over three years since Astwood reported his first three cases, many experienced clinicians in the English-speaking world have tried these drugs, and from all workers favourable reports are coming to hand. With added experience and perhaps with improved forms of the drug, it seems that permanent control of the thyreotoxic factor can be achieved in 85% of cases and that operation now will be confined to some 15%, in which for varying reasons the condition does not respond to the drug therapy.

In THE MEDICAL JOURNAL OF AUSTRALIA of April 13, 1946, S. L. Spencer and I reported a series of 75 patients treated with thiourea and thiouracil, all of whom had been treated and followed for periods varying from six months to two and a half years; in 60 of these cases apparent control of thyreotoxicosis had been established and maintained. Since then a further 25 patients have completed the minimal period of six months. In only one of these cases was drug treatment unsatisfactory and operation required, so that control is apparently effective in 84% of these cases.

With the introduction of methyl thiouracil a new series has been commenced. Of 36 patients, the treatment of 25 has been finalized, although the longest period since cessation of all treatment is only three months. There has been but one unsatisfactory result in this series—the patient was a woman who developed pyrexial reactions and exfoliative dermatitis. Thus results obtained with this compound would appear in this small series to be even better than those obtained with thiouracil.

The response is quicker by some two weeks than that to thiouracil; in the most resistant case so far forty-two days were required for the basal metabolic rate to fall from +75% to −1%, whereas with thiouracil in comparable cases fifty-seven days were required for the basal metabolic rate to fall from +34% to −10% and from +25% to −4%.

Apart from the unsatisfactory case mentioned earlier, the only idiosyncrasies met with were mild febrile reactions in two cases and mild cervical adenopathy in one. There has been no disturbance of the granulocyte cells of the blood and no leucopenia.

So far none of the patients treated with methyl thiouracil have been subjected to operation, as remarkable results have been achieved in the diminution of both exophthalmos and the hyperplastic gland by the administration of *Thyroideum Siccum*, half a grain twice a day; this is given as soon as a *minus* metabolic rate has been established and continued during the maintenance period for some two or three months. In only two cases was it found necessary to administer 0·3 gramme three times a day for some ten days, as the majority of patients respond quickly to 0·1 gramme twice a day for one week and then 0·2 gramme twice a week for two to four weeks, when the basal metabolic rate falls to less than zero. The most important point with regard to maintenance dosage is that the dosage of the drug should be continued at such a level as will maintain a *minus* metabolic rate for a minimal period of three months; this can be attained in the last month or so by 0·05 gramme twice a day.

Pre-Operative Preparation.

In the seventeen cases in which operation was performed, certain technical difficulties have been experienced. As has already been mentioned, patients prepared with thiouracil require less premedication than others and cause no undue concern to the anæsthetist. In the earlier experiences it was noticed that the gland did not strip readily from its fascial capsule (reminding one of iodine perithyreoiditis), and there was considerable oozing of blood from small vessels. The gland itself was difficult to handle, being soft, friable and exceedingly vascular, so that a good deal more blood was lost than usual, and it was not possible to secure the customary exact hæmostasis to allow of closure of the wound without drainage. It was then decided to cease further thiouracil therapy and to administer iodine for the usual ten to fourteen days. This brought about a great change, as the gland became firm and lost its extreme vascularity, and the operation could be completed much more readily. Shortly after this a report came from the Lahey Clinic that similar troubles had been experienced, which were overcome by administering iodine for the three weeks prior to operation coincidently with thiouracil for two weeks and without any thiouracil for the week immediately prior to operation. In a recent report from the Lahey Clinic published in *Surgery, Gynecology and Obstetrics* for October, 1945, it is stated that thiouracil has been used

in the pre-operative management of 190 severely toxic patients since May, 1943. "In addition to eliminating two stage thyroidectomies entirely, deaths which result from so called postoperative thyroid storm or reactions are avoided with certainty." However, workers at this clinic still prepare their patients with mild thyreotoxicosis with iodine, as it is considered that the response is sufficient to permit of operation without risk, and the possible dangers of thiouracil are avoided. It is pointed out that operation should not be performed before the optimum improvement has been obtained, as otherwise anæsthesia is unsatisfactory and an alarming post-operative reaction may occur. In other words, before operation is carried out the general condition of the patient must be satisfactory and the basal metabolic rate within normal limits. At a myxœdematous level sensitivity to sedation and to anæsthesia occurs from depression of the respiratory centre. All patients except those with cardiac breakdown are treated as ambulatory, and it is estimated that the basal metabolic rate will fall 1% each day, so arrangements for entering hospital and the time for operation are calculated accordingly. However, my experience by no means coincides with this mathematical prognostication; often a patient with a relatively low basal metabolic rate (for example, +25%) will take longer to reach a normal level than one with a high basal metabolic rate of, say, +75%.

Carcinoma and Thyreotoxicosis.

It is not uncommon to find that patients with carcinoma of the thyreoid gland also have thyreotoxicosis, and it is important that a correct diagnosis be made, as in most cases deep X-ray therapy controls carcinoma of the thyreoid and also controls coincident thyreotoxicosis.

At the moment of writing I can instance the case of a woman, aged sixty-eight years, who had an adenoma of the right lobe of the thyreoid for over twenty-five years, which was the size of a hen's egg until three months ago. It then began to grow very quickly, and at the time of examination was the size of a clenched fist and adherent to the sternomastoid muscle. Enlarged lymph glands were present in the posterior triangle. The patient exhibited a fine tremor and had lost sixteen pounds' weight in the last eight weeks, during which tachycardia and general nervousness had developed. Her basal metabolic rate was +32% and her basal pulse rate 96 per minute. She is undergoing a course of deep X-ray therapy.

The possible danger of thiouracil in such cases comes from the fact that one experimenter with carcinogenic substances found that he could not produce carcinoma of the thyreoid until coincident administration of thiouracil was tried. This is one reason why patients with toxic adonemata should always be referred for operation, especially if they have been treated with thiouracil.

Conclusions.

1. There is no doubt that in a large number of cases of primary hyperplastic thyreotoxicosis toxicity can be controlled and apparent cure achieved by the intelligent use of thiouracil or methyl thiouracil.

2. As a pre-operative preparation the thio compounds afford a more effective means than iodine for controlling thyreotoxicity and minimizing the operative and post-operative risks.

3. Iodine must be administered for two or preferably three weeks prior to operation, in order to diminish or overcome the technical difficulties encountered if thiouracil alone is used.

4. The anæsthetist must be regarded as an important member of the team in the surgical treatment of thyreotoxicosis.

5. Aspiration of all mucus from the trachea and larger bronchi before the patient leaves the operating theatre minimizes post-operative complications and renders nursing easier.

6. An intelligent appreciation of the bodily requirements and utilization of iodine is essential in the correct preparation of patients for operation.

7. In the thio compounds we have a valuable ally in the treatment of thyreotoxicosis, but one that is not without risks and one that should not be employed unless adequate laboratory facilities are available.

8. All patients with adenoma, single or multiple, of the thyreoid gland should be referred for operation whether toxicity is present or not; but if toxicity is present, their pre-operative preparation with thiouracil is more satisfactory than with iodine.

THE MECHANISMS, LIMITATIONS AND ADVANTAGES OF THE NEWER DRUG THERAPY IN THYREOTOXICOSIS.[1]

By HAROLD J. RITCHIE,
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MR. PRESIDENT and Fellows of the Royal Australasian College of Surgeons, let me first of all thank you for the honour you have done me in inviting me to address you on the subject of drug therapy in thyreotoxicosis, which is new, which is difficult, and which contains many problems yet far from elucidation. I must also ask your patience, inasmuch as the consideration of these drugs and of their effect upon the prognosis of thyreotoxicosis impinges upon the realms of both biochemistry and neurophysiology. I have not made a statistical approach except in the broadest manner, but I shall endeavour to outline the principles underlying this form of treatment.

It is now generally realized that hypersecretion of the thyreoid hormone is usually, if not always, brought about by an over-activity of a special pituitary hormone. This in its turn is strongly influenced by stimuli arising from some of the nuclei of the hypothalamus. The hypothalamus, relatively small in area, is intimately connected with the pituitary gland on the one hand and with the precentral cortex on the other. Cannon, many years ago, defined thyreotoxicosis, with the staring eyes and the general appearance of apprehension, as "a state of continuous terror"—in other words, an over-stimulation of the nuclei of the hypothalamus which control the sympathetico-autonomic system. These symptoms, as you know, are in *formes frustes* part of the symptom complex set up by tumours pressing upon the region of the hypothalamus and by those forms of encephalitis which particularly attack the diencephalon. This would suggest that the strain of pregnancy and lactation, worry and emotional factors, so commonly antecedent to thyreotoxic states, may be transmitted through connexions between the premotor cortex and the hypothalamus, the precipitating cause in many cases of thyreoid over-secretion in primary thyreotoxicosis. This long preamble amounts to a generalization that the surgical attack and, as I hope to show later, the newer form of medical attack by thiouracil and similar drugs, act in the same manner. They do not remove the original cause of the thyreotoxicosis, but by breaking a link in the vicious chain of over-stimulation prevent the disastrous results, both physical and psychic, of long-continued thyreotoxicosis.

A subtotal thyreoidectomy acts by removing the greater part of the gland which is secreting thyroxin in excess. The newer drugs act either by preventing the utilization of iodine by the hyperplastic thyreoid gland or by preventing the final synthesis of thyroxin from diiodotyrosin. To the former group belong thiourea, thiouracil and closely related drugs; to the latter belong the thiocyanates and allied chemicals. The thiouracil group has been most closely studied. The thyreoid takes up a relatively large portion of the iodine which gains entrance to the body. The fate of tracer iodine (that is, radioactive iodine) has been closely studied in animals which have been previously treated with thiouracil. This has served to demonstrate that, instead of the 80% of radioactive iodine demonstrable in controls, 10% or less was present in animals plied with thiouracil.

[1] Read at a meeting of the Royal Australasian College of Surgeons on June 11, 1946, at Sydney.

The affected gland, whether owing to primary or to secondary toxicosis, grows larger, at least temporarily, as a result of over-stimulation by the thyreoid-stimulating hormone of the pituitary gland. This increase in size is due to an intense hyperplastic reaction of the thyreoid, which is almost indistinguishable from that found in glands removed in the pre-iodine days. There is, however, this profound difference, that though the gland is obviously in a state of extreme activity owing to iodine deprivation, little if any thyroxin is being secreted, and in favourable cases the symptoms of thyreotoxicosis rapidly abate. This improvement may be: (*a*) merely a prolonged remission or (*b*) a cure. If operation is not contemplated, it is necessary to give a small and decreasing maintenance dose of the drug. In the bad old days before radical surgical treatment of thyreotoxicosis became general, many of you must remember those pitiable patients presenting a *mélange* of hyperthyreoidism and hypothyreoidism. The overworked thyreoid had passed from activity to fatigue and from fatigue to virtual extinction as a biochemical factor in the body mechanism. It seems reasonable to suppose that thiouracil indirectly excites a beneficial and temporary hyperplasia, in which excess thyroxin is not elaborated, yet fatigue of the thyreoid activity, either temporary or permanent, is produced. The hyperplasia is due to over-stimulation by the thyreotropic hormone of the pituitary gland in an endeavour to cope with the iodine deficiency in the thyreoid itself—a deficiency brought about by the action of thiouracil.

The administration of the drug is surrounded by some difficulties and dangers. Though these are real, they have at times been exaggerated. Any potent drug is a two-edged sword, as the case of the unwise exhibition of the sulphonamides has shown so often. Dosage varies with the individual case and cannot be standardized. An amount of thiouracil which is barely sufficient to control the symptoms of one patient may precipitate another into the physical and mental twilight of temporary myxœdema. Individual idiosyncrasy plays a part in the more serious complications of the therapy. This, it must be remembered, is common to a number of useful and necessary drugs, including the sulphonamides. Idiosyncratic reactions occur almost invariably within the first six weeks of treatment; they include granulopenia, fever with or without joint pains, and pretibial œdema or swelling of the ankles. Nausea and vomiting are sometimes produced. Dermatitis of various kinds may also occur. This, in some instances, appears to be due to photosensitization of the skin, as may happen with the sulphonamides. I may here interpose a word of warning: since the sulphonamides are also goitrogenic, they should never be given at the same time as thiouracil. If an intercurrent infection occurs, it should, if serious, be treated with penicillin. Granulopenia is rare and is becoming rarer; but if it occurs it should be treated by blood transfusions, liver extract and penicillin. The most serious complication of all is acute and widespread arteriolitis. This occurred in a woman who was being given thiouracil and a large dose of sulphonamide simultaneously.

Patients who have previously had a course of iodine are very resistant to thiouracil medication, and the two drugs should never be given together. If operation is intended after a preliminary course of thiouracil, I would strongly urge the necessity of obtaining the full effect of the drug; when this is obtained, a ten-day course of iodine will reduce the vascularity of the gland and make any operative measures easier. If this course is pursued, the spectre of post-operative thyreotoxic crisis should be banished forever.

In my opinion, the exhibition of thiouracil under controlled conditions should be considered an essential part of pre-operative treatment of thyreotoxicosis except in the mildest cases. In the absence of idiosyncrasy, it may be reasonably claimed that the drug alone will control thyreotoxicosis and in many cases will produce remission, even if at this early date we cannot with absolute certainty speak of cure. One thing, however, is sure—that most patients after the disappearance of symptoms require a small maintenance dose for many months. This can be gradually reduced in size till none is needed. I have a number of patients who are still symptom-free although they have taken no thiouracil for eighteen months or longer.

Early primary thyreotoxicosis as a rule yields readily to thiouracil. The so-called nodular toxic goitre also responds satisfactorily, albeit more slowly; but once response has followed, it needs a much shorter period of maintenance dosage. These drugs have a further disadvantage to those already enumerated as complications of treatment. They all cause further enlargement of the thyreoid, at least for the time being. Hence, on account of pressure effects on the trachea and elsewhere, as well as for cosmetic reasons, operative treatment is still strongly indicated in the presence of persistent and considerable enlargement of the gland. Women "dew-lapped like Thessalian bulls" are very prone to think that the disfigurement outweighs any general physical sense of well-being brought about by treatment.

Just as the body can elaborate areas of extramedullary hæmatopoiesis, so it is highly probable, if not certain, that in some cases cells capable of elaborating thyroxin are present in other tissues. Several workers have shown that thyroxin in varying amounts is present in the blood of both human beings and animals after an undoubted complete thyreoidectomy. That this cannot be attributed to accessory thyreoid glands in the substernal region in the neck or at the root of the tongue has been made reasonably certain in animals at least. The formation of extraglandular thyroxin is the probable explanation of the recurrence of thyreotoxicosis after a patient has undergone repeated partial thyreoidectomy at the hands of a competent thyreoid surgeon. Such patients not infrequently have also had considerable X-ray therapy in addition. This is the class of patient *par excellence* to be given the probable benefits of thiouracil therapy. We are often confronted in practice with patients presenting severe cardiac damage, heart failure and auricular fibrillation, for whom operation at best is hazardous. This group often do extremely well on thiouracil therapy, the heart settles down and the normal cardiac rhythm returns. This treatment is also effective in those rare cases of thyreotoxic myopathy which masquerade as progressive muscular atrophy or *myasthenia gravis*. Next, we come to the group of patients who flatly refuse operation; they now at least may be given a good chance to save body and soul alive, as may those with maniacal and psychotic types of the disease who are encountered from time to time.

A further possible disadvantage of thiouracil therapy is the possible prolonged period of observation and treatment. In the early stages, say for the first month or six weeks, it is necessary to keep the patients in hospital; blood counts, and especially leucocyte studies, are advisable at frequent intervals and the clinician must keep watch for any signs of malaise which may conceivably be attributed to the drug. When the stay in hospital has ended the patient should be examined at regular and not infrequent intervals, as the maintenance dose may require to be diminished or increased. I am not a great believer in estimations of the basal metabolism as usually performed in this country; but such estimations often offer some confirmation of clinical opinion in diagnosis and more particularly in treatment.

The average dose of thiouracil ranges from 0·3 to 1·0 gramme *per diem*. The drug should if possible be given in frequent divided doses, as it is rapidly excreted. Subjective sensations of improvement commonly precede any objective signs. The latter present themselves only when the blood thyroxin level has fallen very considerably. It is often desirable but not essential to give small doses of a sedative simultaneously with thiouracil.

Summary.

Let me now sum up my impressions of the value of thiouracil and related compounds and of what appear to be the general indications for their use.

1. In from 70% to 80% of cases of thyreotoxicosis, whether primary or secondary, the condition can be controlled by these drugs.
2. Prolonged periods of remission probably amounting to cure may be expected in a large number of cases.
3. Relapses, if they occur, yield readily to a further course of treatment.
4. There is strong evidence to suggest that in early cases exophthalmos may diminish or disappear.
5. The thyreoid gland almost invariably becomes enlarged, sometimes greatly, under thiouracil therapy.
6. Surgical intervention is indicated when pressure effects or gross disfigurement occur owing to the enlargement of the gland following the administration of the drug, or when for social or economic reasons rapid relief of symptoms is essential, or when serious toxic by-effects arise from the use of the drug.
7. If operation is decided upon, a full course of thiouracil should precede a short period of iodine administration.
8. Insufficient thiouracil treatment may precipitate a post-operative thyreotoxic crisis.
9. If the patient should prove iodine-resistant after preparation by thiouracil, it is desirable to operate early before the effect of the thiouracil has disappeared, despite any technical difficulties which may be encountered.
10. The indications for thiouracil therapy, whether intended as a pre-operative or as a curative measure, have not as yet been so clearly defined that such treatment should be undertaken except under controlled conditions.

Conclusion.

In conclusion, I should like to thank you for your attentive hearing. Even if I have not succeeded in convincing you that at times a drug may be mightier than a scalpel, I hope that I have at least stimulated your interest in a problem of biochemistry closely related to the surgical attack on thyreotoxicosis.

THE TREATMENT OF THYREOTOXICOSIS BY CONCURRENT ADMINISTRATION OF THIOURACIL AND IODINE.

By IVAN MAXWELL, G. GUNTER and K. SCHWARZ,
Royal Melbourne Hospital, Melbourne.

Introduction.

CONSIDERABLE experience has now been gained in various clinics concerning the value of thiouracil in the treatment of toxic goitre. It is regarded as inhibiting the synthesis of thyroxin either by preventing the conversion of diiodotyrosine to thyroxin or, as has been more recently suggested,[1] by inhibiting an enzyme which has as a primary function the oxidation of iodide to iodine.

In December, 1943, one of the authors (I.M.) of the present paper commenced treating patients suffering from thyreotoxicosis with thiourea (later changed to thiouracil) and iodine. On the advice of Professor V. M. Trikojus both drugs were administered concurrently in all cases from the very beginning of treatment. Trikojus[2] had shown that iodine would inactivate the thyreotrophic hormone (or the thyreoid-stimulating hormone) *in vitro*, and it was reasonable to assume that such an action might occur in the thyreoid.

When thiouracil is given to rats it induces hyperplasia of the thyreoid gland. The reason for this is that as the thyroxin normally liberated from the thyreoid gland diminishes under the influence of thiouracil, the pituitary gland is stimulated to liberate thyreoid-stimulating hormone. This induces hyperplasia of the thyreoid acinar cells, but is unable to cause synthesis of thyroxin. The gland enlarges and becomes more vascular and friable. If in man iodine could prevent this thiouracil-induced hyperplasia by interfering with the action of thyreoid-stimulating hormone, then the patient might be prepared for operation more expeditiously and more satisfactorily from a surgeon's standpoint. Furthermore, the prolonged use of the two drugs might give therapeutic results unobtainable by the use of each separately.

This, then, was the line of reasoning responsible for the concurrent use of these drugs in 1943, and which has been continued as the routine treatment ever since. The problem has been recently discussed by Wright and Trikojus[3] (1946) in reference to the mode of action of iodine in thyreoid disease.

General.

Of the 56 patients suffering from thyreotoxicosis reviewed in this paper, 52 were females and four males. After preliminary treatment with thiouracil and iodine given concurrently subtotal thyreoidectomy was performed in 19 cases. Medical treatment only was given to 37 patients. In Figure I it will be observed that most of the patients' ages fell between twenty and fifty years.

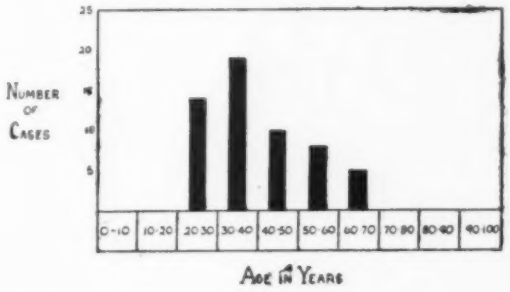

FIGURE I.
Showing age incidence.

Basal Metabolic Rate.

All except six patients were confined to bed during their pre-operative treatment, or in the early stage of what we may describe as long-term medical treatment. Basal metabolic estimations were performed after twenty-four or forty-eight hours' rest and were repeated in a week's time, during which period the patients had rest in bed with sedation (usually produced by means of phenobarbital). Thiouracil and iodine therapy was not commenced until the effect of rest and sedation on the basal metabolic rate, sleeping pulse and weight had been observed. If Table I is studied and Figures II and III are compared, it will be noted that rest and sedation had a considerable effect in reducing toxicity as measured by basal metabolic estimation. Allowance for this is frequently overlooked in various contributions to the literature. If thiouracil and iodine had been administered to the patients immediately on their admission to hospital, more credit would have been given to the drugs than they deserved. For comparison with Figures II and III is Figure IV, in which is indicated the intensity of the basal metabolic rate after three weeks of treatment with thiouracil and iodine. In Figure V it will be noted that the average basal metabolic rate prior to rest and sedation was +36%, whilst after seven days of such treatment it had fallen to +18% and had further fallen to +4% in fourteen days of treatment with thiouracil and iodine. In Figure VI are charted the detailed response of a patient to the administration of thiouracil and iodine. From Table I it will be noted that quite a number of patients had, on entering hospital, a basal metabolic rate of +50% or more.

Gain in Weight.

During the week of rest prior to the use of thiouracil and iodine the patients not only failed to gain in weight, but the average loss of one and a half pounds per person occurred. This was followed by a steady gain in weight as thyreotoxicity diminished. Among those treated medi-

TABLE I.

Chart of Patients Treated with Thiouracil and Iodine (Without Surgery).[1]

No.	Initials.	Basal Metabolic Rate on Admission to Hospital.	Before Treatment.			After Treatment.			Duration of Treatments (in Months).	Time Since Cessation of Treatment (in Months).[2]	Results and Comments.
			Basal Metabolic Rate After Seven Days' Rest and Sedation.	Weight.	White Cell Count per Cubic Millimetre.	Basal Metabolic Rate.	Weight.	White Cell Count per Cubic Millimetre.			
				st. lb.			st. lb.				
1	B.B.	+20%	+12	10 3	15,000	−21	10 2	9,150	3	5	Very good.
2	H.B.	+64%	+44	8 9	5,900	+16	9 2	4,000	7	0·5	At first the patient progressed very satisfactorily, but later developed thiouracil sensitivity. Treatment with iodine only was followed by thyreoid resection.
3	G.B.	+26%	(*a*) +15 (*b*) +42	9 6 8 13	5,800 6,000	−10 +1	9 6 9 10	7,600 6,400	(*a*) 2 (*b*) 4	— C	After two months of therapy (*a*) the patient discontinued treatment for four months. Thyreotoxic symptoms returned (basal metabolic rate +42%), but were again controlled by thiouracil *plus* iodine and basal metabolic rate returned to +1.
4	O.B.	+72%	+65	10 5	8,400	+16	10 12	9,000	5	—	Thiouracil caused pyrexia. Patient responded very well to iodine *plus* thiourea.
5	D.C.	+30%	+10	7 8	5,500	−8	7 13	5,500	4	C	Very good.
6	E.C.	+71%	+46	8 9	11,000	−2	10 6	6,500	26	2	Very good.
7	I.D.	+59%	+47	9 12	5,400	+14	11 6	7,000	13	18	Excellent.
8	M.F.	+54%	+50	9 3	23,000	—	8 12	15,000	0·3	—	Thiouracil caused pyrexia. Patient prepared with iodine and submitted to subtotal thyreoidectomy.
9	M.G.	+18%	+16	6 2	5,000	−4	7 12	6,000	9	C	Very good.
10	E.H.	+45%	+19	9 1	8,500	+8	8 2	6,000	14	C	Very good.
11	F.H.	+22%	+4	9 11	7,000	±0	8 7	6,300	8	C	Good.
12	J.H.	+24%	—	—	11,200	+3	—	9,300	2	—	Good.
13	F.H.	+34%	+29	—	9,000	+12	—	9,600	2	—	Very good.
14	J.J.	+64%	+54	10 8	10,000	+10	10 9	5,700	23	5	Excellent.
15	M.K.	+48%	+35	9 12	7,700	+14	9 4	7,700	1	—	Fair. Patient returned to country.
16	M.L.	+62%	+63	10 7	8,800	+10	11 13	10,000	25	C	Excellent.
17	A.N.	+30%	—	9 3	6,100	−14	10 10	8,000	3	2	Very good.
18	M.P.	+51%	+20	8 13	6,500	−10	9 4	7,150	3	—	Thiouracil discontinued as exophthalmos developed during course of treatment.
19	E.Q.	+28%	+6	8 5	8,000	±0	9 0	12,700	26	1	Excellent.
20	R.S.	+36%	+30	8 10	8,000	+5	10 13	8,500	12	12	Very good whilst taking iodine only, after recovery from agranulocytosis.
21	G.S.	+59%	+44	8 12	6,800	−20	9 11	15,000	10	C	Excellent.
22	V.S.	+83%	+34	10 0	7,000	+8	9 13	6,500	7	C	Excellent.
23	F.S.	+54%	+28	8 12	—	+15	9 10	—	2	—	Very good. Patient did not return for further treatment.
24	A.T.	+52%	+18	7 6	6,050	+4	6 7	5,000	12	3	Patient developed agranulocytosis, but recovered, and is now very well whilst taking iodine only.
25	N.T.	+44%	+30	9 1	7,000	+18	9 11	5,000	2	C	Very good.
26	R.T.	+59%	+47	7 0	7,000	−10	7 11	7,000	4	C	Excellent.
27	V.T.	+8%(?)	+24	8 12	7,200	+14	8 3	5,700	8	C	Good. Patient feels well.
28	E.W.	+68%	+7(?)	9 0	5,000	+19	9 11	7,500	1	—	Good.
29	M.W.	+69%	+45	10 7	11,000	+31	9 12	12,000	7	5	Patient discontinued treatment without permission.
30	M.W.	+35%	+10	6 8	10,000	+1	7 5	6,100	5	C	Very good.
31	A.M.	—	+29	8 7	8,000	−4	8 5	4,400	19	C	Very good.
32	A.D.[3]	—	+45	9 7	8,600	−13	10 10	6,800	3	C	Excellent.
33	J.D.[3]	—	+20	9 8	8,200	+2	9 11	7,000	5	C	Very good.
34	B.F.[3]	—	+60	9 3	9,500	+24	9 11	11,200	8	C	Very good.
35	E.G.[3]	—	+39	10 0	5,000	±0	10 2	6,500	12	1	Excellent.
36	R.H.[3]	—	+52	9 7	8,500	+2	10 5	9,000	13	C	Excellent.
37	J.M.[3]	—	+16	10 0	8,300	−9	9 13	6,300	16	C	Very good.

[1] The object was to treat this series of patients entirely medically. In two cases this object was not achieved, and it was necessary to resort to surgery.
[2] "C" indicates treatment continuing.
[3] Ambulatory treatment.

cally for many months the gain was frequently twenty pounds or more. The patients looked and were remarkably well.

The Sleeping Pulse Rate.

The influence of rest and sedation is well seen in Figure VIII. The average sleeping pulse rate was reduced from 90 to 80 in one week and a further reduction to normal occurred in two more weeks by the use of thiouracil and iodine.

Dosage.

Thiouracil was usually administered in an initial dose of 0·6 gramme, divided into three parts of 0·2 gramme given before meals. It was occasionally thought desirable to prescribe a larger initial dose; hence in Figure IX the average dose of thiouracil during the first week was 0·62 gramme. Reduction in dosage was determined by the improvement of the patient. If subtotal thyreoidectomy was not performed a daily maintenance dose, usually of 0·05 to 0·2 gramme, was prescribed.

Iodine was administered in the form of Lugol's solution. Five minims thrice daily was the initial dose, and this was reduced after ten days or so to one minim twice daily to be continued along with thiouracil as a maintenance dose. The Lugol's solution was given in milk after meals so that at least an interval of one hour separated the ingestion of iodine and of thiouracil. These facts are indicated in Figure IX.

Toxic Symptoms due to Thiouracil.

Toxic symptoms due to thiouracil may be enumerated under the following five headings.

Joint and Muscle Pains and Swellings.—Joint and muscle pains and swellings occurred in nine patients. They disappeared on discontinuance of the thiouracil for a few days. They did not reappear on resumption of the previous dosage.

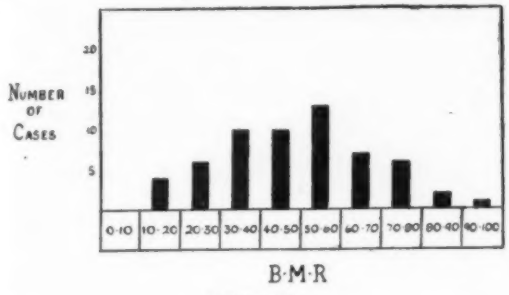

FIGURE II.

The basal metabolic rate on the patient's admission to hospital.

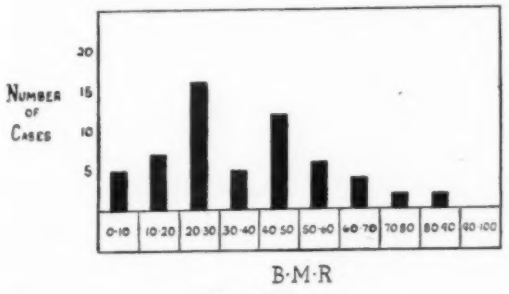

FIGURE III.

The basal metabolic rate after one week's rest and sedation.

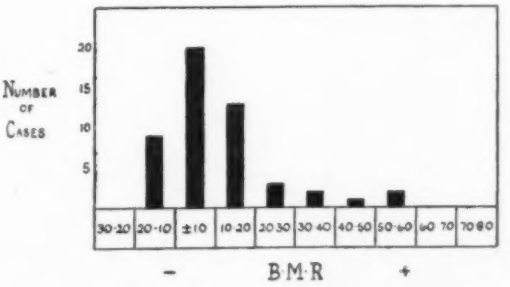

FIGURE IV.

The basal metabolic rate after three weeks of treatment with thiouracil and iodine concurrently.

Leucopenia.—Leucopenia was guarded against by blood examinations at intervals varying from one to four weeks. Any count below 4,000 white blood corpuscles per cubic millimetre was taken as an indication to stop the use of thiouracil. Administration was resumed when the counts returned to normal, which was usually in a week or two. The variation in white cell count is shown in Figure X.

Agranulocytosis.—Agranulocytosis occurred in two patients. In each instance treatment had been progressing satisfactorily. In one patient skin infections on the hand and legs suggested a further examination of the blood, when agranulocytosis was discovered. Discontinuance of thiouracil, rest in bed and administration of much fluid were followed by return of the white count to normal. The subsequent treatment was with iodine, and the patient, some months later, is now very well and has a normal basal metabolic rate and pulse rate, and has gained several pounds in weight.

The second patient developed a white cell count of 1,400 per cubic millimetre. The procedure was to admit the patient to hospital, to stop thiouracil and to administer 15,000 units of penicillin intramuscularly every three hours. This patient was sixty-two years of age. She made a rapid recovery. She may need subtotal thyreoidectomy, but is anxious to avoid operation, and as she is well whilst taking iodine, this is being continued.

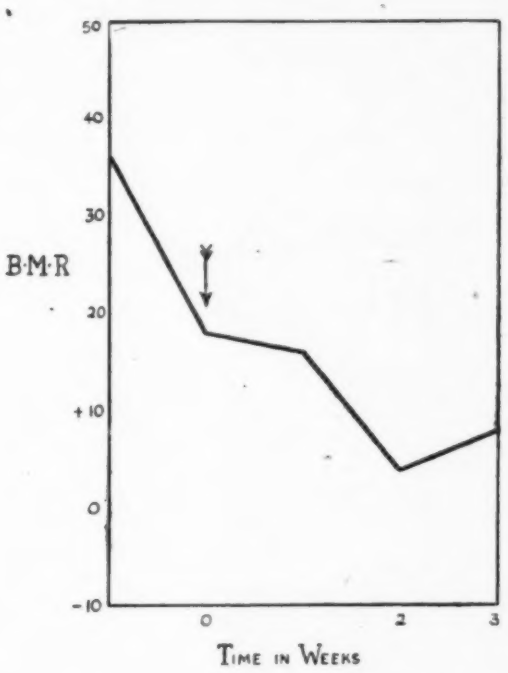

FIGURE V.

Response of the basal metabolic rate to rest and sedation (left of arrow) and thiouracil with iodine (right of arrow). The graph represents average response.

Pyrexia.—Two examples of pyrexia have occurred. In the first instance discontinuance of thiouracil caused the pyrexia to subside, but it returned when thiouracil was given again and subtotal thyreoidectomy was performed after preparation of the patient with iodine only. The second patient had had resection of the thyreoid gland some ten years before reporting on this occasion to the Royal Melbourne Hospital. It was thought desirable to try medical rather than surgical treatment. This at first proceeded very satisfactorily, but without warning the temperature of the patient rose to 103° F. Thiouracil was discontinued and the temperature fell to normal in two days, but pyrexia recurred when the drug was again administered a week later. Thiouracil was now permanently discontinued and thiourea was given as a substitute. This caused no toxic disturbance and the patient's thyreotoxicosis is now controlled by a maintenance dose of thiourea and Lugol's solution.

Other Evidences of Toxicity.—Other indications of toxicity caused by thiouracil were nausea, a rash, and in one instance cellulitis of the leg. None of these proved of serious moment.

Selection of Patients for Thyreoid Resection.

The following groups of patients need surgical rather than prolonged medical treatment.

1. Those with large toxic goitres, particularly the nodular type. Even if the thyreotoxicosis responds to medical treatment, it is unlikely that the gland will diminish much in size; it remains an unsightly reminder of the disease and has a bad psychological effect on the patient.

2. Those who have evidence of pressure on surrounding structures. The trachea may be pressed upon or retrosternal extensions of the goitre may cause embarrassment

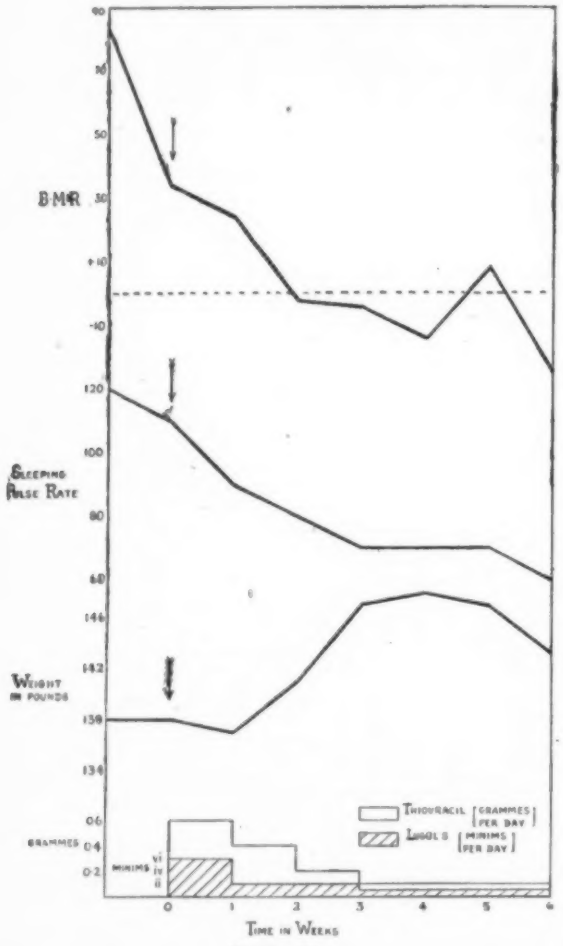

FIGURE VI.

Detailed response of a patient to the administration of thiouracil and iodine given concurrently.

within the thorax. In such cases the swelling of the gland may be increased at least temporarily by thiouracil administration. Such an effect is undesirable.

3. Patients who live in the country far from medical aid. It is unwise to allow patients to continue taking thiouracil without blood examinations (white cell counts) at regular and fairly frequent intervals. Such examinations should be performed at least once per month and in some cases more frequently. Furthermore, any feeling of ill health should be reported by the patient at once.

4. Those with indications of malignant changes in the thyreoid gland.

5. Those showing toxic manifestations due to thiouracil therapy. The development of agranulocytosis is an indication for surgery—after restoration of the patient—rather than for the continuance of medical treatment.

6. Those patients who are of comparatively low mentality and who have difficulty in appreciating the necessity for prolonged medical treatment.

Nineteen patients whose classification fell into one or other of the above groups were submitted to subtotal thyreoidectomy. The results of surgical treatment were excellent in all except two cases. In one of these recurrence of symptoms took place, but these have now been successfully controlled by thiouracil *plus* iodine. The other patient died in a post-operative crisis. To avoid misconception concerning the efficiency of thiouracil and iodine in the pre-operative treatment of thyreotoxicosis, a few words of explanation concerning the circumstances associated with the treatment of this patient are necessary.

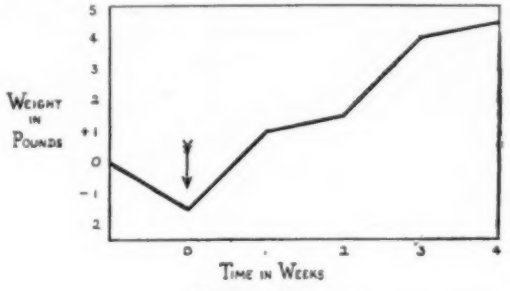

FIGURE VII.

Effect on weight of treatment with thiouracil and iodine (right of arrow), rest and sedation (left of arrow). Average response.

When first admitted to hospital he suffered from severe thyreotoxicosis (basal metabolic rate +52%). Thiouracil and iodine promptly and satisfactorily controlled the condition. On his leaving hospital a maintenance dose of thiouracil and iodine was prescribed. After reporting regularly for a few weeks he discontinued attending hospital. He next appeared four months later, accompanied by a police officer from a penal establishment, where he had been serving a sentence. He had had no treatment for all these months and was again very thyreotoxic (basal metabolic rate +84%). He again quickly responded to treatment with thiouracil and iodine. As a police officer was stationed at the hospital guarding the patient day and night, it was regarded as urgent to perform thyreoid resection at the earliest possible moment consistent with the safety of the patient.

Had the circumstances been different, pre-operative treatment would have been continued longer and the risk, which was thought justifiable, would not have been taken. (The basal metabolic rate prior to operation was +24%.)

When the groups of patients enumerated above have been transferred to the surgeon there still remain: (*a*) those who have a relatively small toxic goitre associated with marked thyreotoxicosis—the intensity of thyreotoxicosis is not a contraindication to medical treatment; (*b*) those who have a small goitre associated with a slight degree of toxicity.

These two groups of patients are suitable for medical treatment, and surgical operation on them is necessary only if such treatment fails. However, it must be realized that the treatment is long and carries with it a small degree of risk owing to toxic disturbances arising from abnormal reaction to thiouracil.

Of 247 patients suffering from thyreotoxicosis and treated with thiouracil, Williams found it necessary to submit 121 to thyreoidectomy. Of the remaining patients, 100 were treated with thiouracil for many months. Of these, 51 exhibited a relapse of symptoms of the disease on discontinuing therapy. These figures from the clinic of one

who has had much experience, indicate the need for great care on the part of any practitioner who undertakes the medical treatment of toxic goitre.

The Effect of Thiouracil Plus Iodine on the Histology of the Thyreoid in Thyreotoxicosis.

The effect of thiouracil *plus* iodine on the histology of the thyreoid gland in thyreotoxicosis is shown in the following cases.

L.B. on admission to hospital had a basal metabolic rate of +40%. Two days later a biopsy was performed on the thyreoid gland. This pre-operative specimen on histological examination showed a marked epithelial hyperplasia, little colloid was present (and that granular in character) and there were no signs of involution in the gland. The gland was vascular and lobulated (Figures XI and XII).

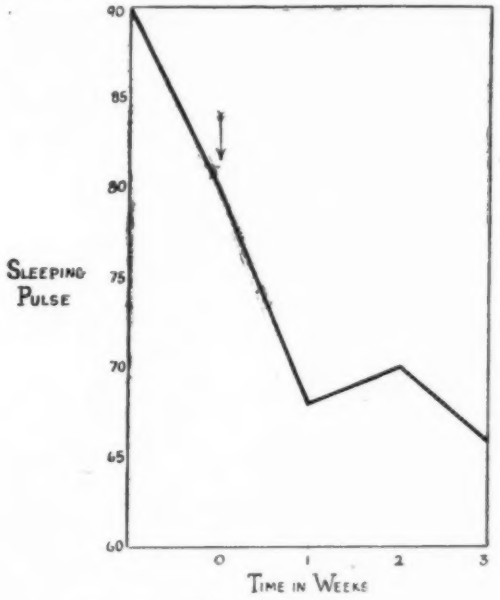

FIGURE VIII.

Influence of rest and sedation (left of arrow). Effect of thiouracil and iodine (right of arrow). Average response.

Following the biopsy the patient was immediately treated with Lugol's solution, a start being made with fifteen minims thrice daily; the dose was gradually reduced to three minims thrice daily. Thiouracil was given concurrently, a start being made with 0·6 gramme daily. In eighteen days the basal metabolic rate was −2%. It was now planned to perform a subtotal thyreoidectomy, but owing to a slight infection of the line of suture of the biopsy wound, this had to be postponed for a month. The patient spent some of this time at home. She continued with a maintenance dose of thiouracil—0·1 gramme twice daily and Lugol's solution three minims twice daily. A few days before the thyreoid resection, the basal metabolic rate was +2%. The histological report on the specimen obtained at operation was: "Well-marked involution, traces of epithelial hyperplasia." The comparison of these sections obtained before and after treatment with thiouracil and iodine shows most convincingly the storage of colloid and the diminution of hyperplasia under the influence of these two drugs. (See figures XIII and XIV.)

In a report by Rawson *et alii*[1] it is emphasized and illustrated by photomicrographs that thiouracil administered alone actually increases the hyperplasia and hypertrophy seen in hyperthyreoidism and does not induce colloid storage in the thyreoid gland. Hence the gland at operation is friable and bleeds readily. The thyreoid gland prepared for operation by the combined use of thiouracil and iodine is free from these objections. It is firm, has stored colloid, is not hyperplastic, and is easy to handle operatively.

The photomicrographs of tissue from the patient E.S. (Figures XV and XVI) show a similar colloid storage after treatment with thiouracil and iodine. At the time of admission to hospital her basal metabolic rate was +68%, and after a week of rest and sedation this was reduced to +28%. After two weeks' treatment with thiouracil and iodine the rate had fallen to +11%. The patient was discharged from hospital on a daily maintenance dose of 0·2 gramme of thiouracil and two minims of Lugol's solution. Four months later the basal metabolic rate was +8% and the patient was very well. At this juncture the patient decided to live in the country, far from medical attention. It was thought desirable to perform subtotal thyreoidectomy. The pathologist's report on the histology of the resected gland was: "Well-marked involution with accumulation of colloid, traces of epithelial hyperplasia."

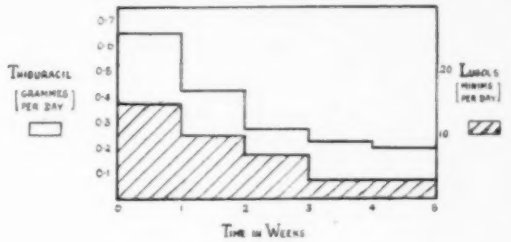

FIGURE IX.

The dosage of thiouracil and iodine.

Many further instances of satisfactory involution of the thyreoid gland whilst the patient was taking thiouracil and iodine concurrently could be cited.

It is of interest at this stage to quote the findings of Rawson *et alii*[1] on the use of thiouracil and iodine in the treatment of toxic goitre.

> It appears (1) that under thiouracil treatment the hyperplastic thyroid gland of Graves' disease becomes yet more hyperplastic, (2) that thiouracil prevents the utilisation of iodine by the thyroid, (3) that notwithstanding this block to the collection of iodine produced by thiouracil iodine causes involution of the thyroid gland in Graves' disease. Therefore, it is concluded that iodine exerts two actions upon the thyroid gland in Graves' disease, an iodinating action and an involuting action, and that these two actions can be separated one from the other by means of thiouracil.

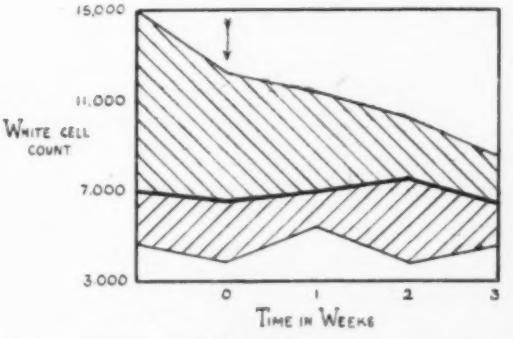

FIGURE X.

This graph depicts the highest, lowest and mean of the white cell count. To the left of arrow is shown the effect of rest and sedation, to the right the effect of thiouracil and iodine given concurrently.

Discussion.

When iodine is administered to a thyreotoxic patient according to the pre-operative procedure introduced by Plummer, thyreotoxicosis is usually rapidly controlled. If operation is not performed at this stage of improvement, the thyreotoxic state once more slowly becomes manifest. Means contends that thyreotoxicity is still partially con-

trolled by the iodine which acts as a "brake"—not, however, a completely efficient one. If the "brake" is removed (that is, if iodine administration is discontinued) and thiouracil is substituted, the patient has a temporary exacerbation of symptoms because it takes some time for thiouracil to show its effect. If, however, the iodine administration is continued along with thiouracil, the basal metabolic rate falls slowly, because there is much stored thyroxin in the thyreoid gland which has to be dispersed before toxicity disappears. Astwood[4] claimed that the administration of iodine and thiouracil together is usually contraindicated, but two of his patients who had received iodine prior to thiouracil did respond normally, and in only these two cases was the administration of iodine continued with the thiouracil, as is our custom.

In cases of primary Graves's disease treated with both iodine and thiouracil from the very beginning of therapy, a rapid diminution of synthesis of thyroxin is induced by the latter drug with a storage of colloid and a restraint of hyperplasia by the iodine. An ideal pre-operative result is obtained from a surgeon's standpoint and an excellent beginning from the physician's angle if he wishes to try prolonged medicinal control of the condition. Rawson[5] compared the histological appearance of biopsy specimens taken prior to thiouracil treatment with those obtained from the gland at operation after thiouracil therapy. Hyperplasia was more evident after thiouracil treatment and involution was particularly inconspicuous. This is in marked contrast to our own experience in the concurrent use of thiouracil and iodine (see Figures XIII, XIV, XV, XVI). Colloid storage was produced quite consistently in our series. Our experience has been confirmed by Lahey *et alii*,[6] who state:

> When the first patients receiving thiouracil underwent thyroidectomy a most unsatisfactory surgical complication was encountered. The thyroid gland was found to be soft and friable and bleeding of the entire operative site was so extensive that there was difficulty in keeping the field sufficiently dry to carry out the usual surgical technique.
>
> The friability of the thyroid gland was overcome when Lugol's solution was administered during the three week period immediately before operation.

Williams[7] observed in 89 patients the effect of iodide when it was associated with thiouracil in various ways. He concluded:

> Of the various systems of treatment used it was found that technical difficulties (in thyroid operations) were least when potassium iodide was used before and during the thiouracil treatment.

Attention should be drawn to the fact that Lahey *et alii* state:

> Approximately one day of treatment with 0·6 gram thiouracil is required for each percentage of elevation in the basal metabolic rate. For example, a patient with a basal metabolic rate of +55 will require approximately 55 days of thiouracil therapy to bring the basal metabolic rate to normal.

Our experience is that thiouracil and iodine given concurrently from the commencement of treatment would in most cases reduce such a basal metabolic rate to normal in fifteen to twenty days.

We do not agree with the statement of Poate and Spencer[8] "that iodine should not be given during treatment with thiouracil". Their contention is not confirmed by the most recent findings in important thyreoid clinics in the United States of America, nor is it supported by our own experience.

The economic aspect of medical treatment must not be forgotten. It necessitates a considerable number of visits to the physician over a long period, with loss of time from work if the patient is a wage earner. This must be contrasted with the comparatively short duration of surgical convalescence. The mortality from surgical resection of the thyreoid gland varies from as low as 0·3% in the hands of the most skilled surgeons to 4% or 5% in the practice of those not so specialized in goitre surgery. The mortality in some 6,000 patients treated medically in the United States of America was 0·5%. These deaths were due to agranulocytosis. There is no doubt that thiouracil is very effective in controlling thyreotoxicosis. There is also no doubt that the treatment is long, requires considerable skill and judgement in its control, and is associated with a varying degree of toxic disturbance affecting almost 10% of patients treated. Already other drugs of a less toxic character are being tried,[9] including methyl thiouracil, ethyl thiouracil and propyl thiouracil ("Probacil"), and it is reasonable to suppose that with further advances in chemotherapy more toxic goitres will be treated satisfactorily by medical means. It is, however, likely that unless a prophylactic treatment of toxic goitre is developed, the fully established disease will remain at least in part a surgical problem for many years to come.

Conclusions.

1. Thiouracil and iodine administered concurrently are of the greatest value in the pre-operative treatment of most patients suffering from toxic goitre.
2. The combined use of these drugs is to be preferred to their individual use.
3. Whilst pre-operative therapy is the chief function of the concurrent use of these drugs, excellent results may be obtained in selected cases treated non-surgically by the prolonged use of thiouracil and iodine.
4. Toxic disturbances due to thiouracil render this method of treatment not without risk.

Acknowledgements.

We should like especially to thank Miss Beryl Splatt, to whom we are indebted for all the biochemical investigations referred to in this paper. To Dr. Hilda Gardner and her staff we are most grateful for the innumerable white cell counts performed on our patients. We remember with much appreciation the late Dr. R. J. Wright-Smith, who was responsible for valuable advice concerning the interpretation of the histological specimens. Mr. Guthrie, of the Department of Pathology, University of Melbourne, prepared the photomicrographs, and to him we express our thanks for his expert work. We should like also to acknowledge our debt to the nursing staff of the Royal Melbourne Hospital, who gave us valuable assistance in our work in the wards. Lastly, our sincere thanks are due to the Lederle Laboratories, Incorporated, New York, for their very generous gift of "Deracil" (thiouracil), which was used in these investigations. A further gift of "Probacil" has just been received.

Legends to Illustrations.

FIGURE XI.—L.B. Photomicrograph (× 250) of thyreoid obtained before treatment.

FIGURE XII.—L.B. Photomicrograph (× 650) of thyreoid obtained before treatment.

FIGURE XIII.—L.B. Photomicrograph (× 250) of thyreoid obtained at operation after treatment with thiouracil and iodine.

FIGURE XIV.—L.B. Photomicrograph (× 650) of thyreoid obtained at operation after treatment with thiouracil and iodine.

FIGURE XV.—E.S. Photomicrograph (× 250) of thyreoid obtained at operation after treatment with thiouracil and iodine. Basal metabolic rate on admission to hospital, +68%.

FIGURE XVI.—E.S. Photomicrograph (× 650) of thyreoid obtained at operation after treatment with thiouracil and iodine. Basal metabolic rate on admission to hospital, +68%.

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METHYL THIOURACIL IN THYREOTOXICOSIS.[1]

By HUGH R. G. POATE,
Sydney.

IN THE MEDICAL JOURNAL OF AUSTRALIA of April 13, 1946, S. Livingstone Spencer and I reported our experiences with thiourea and thiouracil in 75 cases of thyreotoxicosis. In sixty of these an effective control of the thyreotoxicosis appeared to be achieved, which had lasted from six to twenty-one months without any sign or symptom of relapse. No case was included in which treatment had ceased less than six months previously, and all patients were checked to February, 1946. Since that date a further 25 patients have concluded treatment with thiouracil and passed the six months' period since its cessation with only one unsatisfactory result, so that of 100 cases in which treatment was given with the two thio compounds mentioned, a satisfactory clinical result was obtained in 84.

It was stated in the previous report that a supply of methyl thiouracil had been received by courtesy of Messrs. Genatosan, Limited, and this, with further supplies received from Messrs. May and Baker and from Andrew's Laboratories, of Sydney, has enabled the treatment of 38 patients to be completed with this compound and sufficient time to have passed to exclude any possible relapse.

Principles of Treatment.

In the light of added experience, one can now say that a definite plan of treatment must be followed, allowance being made for variations according to the clinical condition of the patient.

Before any thiouracil or methyl thiouracil is administered, it is necessary to have a leucocyte count made; if the initial number of leucocytes is low, a close watch is necessary to forestall leucopenia or possible agranulocytosis. In most cases the count rises in the first month and may then fall slowly below the initial count; but it is unnecessary to modify treatment unless the number of leucocytes falls below 4,000 per cubic millimetre and the percentage of neutrophile cells below 40. If this level is reached, some potent liver extract should be given by mouth, as this should prevent any further fall. It is advisable to check the number of leucocytes every week for the first six weeks, and then every fortnight until the maintenance dose has been established, when monthly counts should suffice.

Estimations of the basal metabolic rate are not so necessary in the early stages except as a matter of interest and to check the rate of progress; but they are of importance when the stage of determining the maintenance dose has been reached. It seems imperative if long-continued or possibly permanent control of thyreotoxicosis is to be achieved that a *minus* metabolism between zero and −15% must be maintained for a minimum period of three months and preferably for four months before treatment can be suspended without risk of relapse. It is obvious, from the reading of current literature as well as from discussions with one's colleagues, that this vital principle has not become generally known, for there are many reports of recurrence of thyreotoxicosis, usually within two months, if treatment is suspended as soon as the basal metabolic rate falls to normal.

Adjuvant therapy depending on the clinical condition of the individual is a necessary part of treatment. In all cases regular sedation and the administration of some mixed vitamin preparation are advisable. In the presence of very acute thyreotoxicosis some alkali should be given until the basal metabolic rate falls, and if the leucocyte count is below 5,000 per cubic millimetre, liver should be given until it rises or becomes stabilized.

Dosage.

The best dose of thiouracil is the minimal dose which will induce a satisfactory response, and there can be no fixed dosage such as is advocated by so many clinics, chiefly those in the United States of America. One can say now that the optimum commencing dose of methyl thiouracil or thiouracil is 0·1 gramme three times a day. This is continued for seven to ten days, when 0·2 gramme may be given if the response has not been adequate, and this dose is maintained until the basal metabolic rate falls to near zero, when 0·1 gramme three times a day is given until a *minus* metabolism develops. In many cases it will be found unnecessary to exceed the 0·1 gramme dose, and in a very few cases 0·3 gramme may be needed for one or two weeks. Patients should report every two weeks for the first two months and then every three or four weeks.

Once a *minus* metabolism is established, the dose of 0·1 gramme three times a day should be continued for three or four weeks—that is, until the next estimation of the basal metabolic rate. If this is still below zero, the dose should be reduced to 0·1 gramme twice a day for four weeks. If the basal metabolic rate is still below zero, a dose of 0·05 gramme twice a day should hold it so for another month or preferably two months, when thiouracil treatment may be discontinued.

It is advisable to insist that patients report after this at intervals of two months for six months, as some sedation or other adjuvant therapy may still be necessary. The majority of patients can be treated as ambulatory without interference with their work; but in very severe cases, usually if the patient is elderly or if fibrillation has occurred, treatment in hospital may be advisable for the first four to six weeks.

With the form of minimal dosage as outlined there is seldom any increase in the gland hyperplasia, and idiosyncrasies or toxic reactions are few and of minor grade. Permanent control of thyreotoxicosis can be expected only if the condition is of the acute primary type, and the gland is of the uniformly enlarged, smooth, hyperplastic variety best exemplified in acute Graves's disease of young people.

If any pronounced enlargement of the gland and any exophthalmos are present at the commencement of treatment, these usually respond, provided they are not of more than six months' duration, to the administration of half-grain doses of *Thyroideum Siccum* twice a day as soon as the *minus* metabolism has been established, and this dosage is continued during the whole maintenance period.

Patients with old colloid goitres which have become toxic or with adenomatous (nodular) toxic goitres, do not respond so quickly or so satisfactorily as those with the primary hyperplastic type, and should all be referred for operation when the basal metabolic rate is within normal limits, provided the general condition permits of it, and provided also that the patients are willing to submit to operation. Otherwise, these patients may require indefinite maintenance on 0·1 or 0·2 gramme of thiouracil per day.

Occasionally a patient with a large hyperplastic gland which has not resolved with treatment desires operation for cosmetic reasons; but in such cases one should not be so radical as with iodine preparation, otherwise some degree of myxœdema may result.

It must always be remembered that patients who have had iodine administered are much slower in their response to thiouracil, and the more recently the iodine has been given, the greater is this lag period.

[1] Part of an address given at a meeting of the Royal Australasian College of Surgeons on September 11, 1946, at Adelaide.

Results with Methyl Thiouracil.

A more detailed examination of the 38 cases in which treatment with methyl thiouracil has been concluded may now be undertaken. There were five male patients and 33 female patients whose ages ranged from sixteen to sixty-four years; but the majority were aged between twenty-five and forty-five years. The patients were distributed as follows: (i) patients aged under twenty years (two females); (ii) patients aged between twenty-five and forty-five years (one male, nineteen females); (iii) patients aged over forty-five years (two males, five females); (iv) patients with toxic adenoma (three females); (v) patients with recurrent thyreotoxicosis after operation or X-ray therapy (two males, four females).

Toxic Reactions.

There was one case of mild cervical adenopathy and one of mild febrile reaction, treatment being stopped for forty-eight hours. One female patient had a recurrence of exfoliative dermatitis, which appeared to be an allergic manifestation influenced by bromide and phenobarbital rather than caused by methyl thiouracil. Her original leucocyte count was 5,000 per cubic millimetre, the percentage of eosinophile cells being 11; after eighteen days the count rose to 8,000 per cubic millimetre and 18% eosinophile cells, and a week later to 8,000 per cubic millimetre and 24% eosinophile cells, although all treatment had been stopped on the fifteenth day. This case will be fully reported elsewhere.

The Leucocytes.

Twenty-six patients had a relative leucocytosis after three or four weeks' treatment, and in twelve cases the number of leucocytes dropped by 1,000 to 2,000 per cubic millimetre from the original count; but in no case did the number fall below 4,500 per cubic millimetre nor the neutrophile percentage below 50.

In the majority of cases there was a decided increase in the percentage of eosinophile cells, in some up to 10%.

General Results.

Two patients were operated on, one being the woman who had exfoliative dermatitis and the other being a woman who had a myasthenic type of thyreotoxicosis supervening on an old colloid goitre, although toxicity had been controlled and she had put on forty-five pounds in weight.

When all cases are considered, the average time for an adequate response to a zero or *minus* basal metabolic rate was just over six weeks, the average drop being 32%. When the response of the thirteen patients previously treated with iodine is compared to that of the 25 patients who had received no iodine, the average time of adequate response was nine weeks as against four and a half weeks, although the average drop in the basal metabolic rate remained the same, namely, 32%. This delayed response did not occur in all the cases in which previous treatment with iodine had been given, but in the majority it was definite, and it confirms the findings of other observers using thiouracil.

The average gain in weight was sixteen pounds, the maximum being over forty pounds in two cases.

There were three cases of auricular fibrillation, and in each normal rhythm was established in three to four weeks.

In sixteen cases *Thyroideum Siccum* in half-grain doses twice a day was given as soon as a *minus* metabolic rate was obtained, so as to control exophthalmos, to reduce the size of the hyperplastic gland and to obviate the onset of myxœdema. In twelve cases in which the condition had been present for only three to five months, the exophthalmos cleared and the gland became normal; but in the other four there was a long history, and although improvement occurred the patients' condition did not return to normal.

In giving the *Thyroideum Siccum* it is necessary to watch the metabolic rate, and if it shows any tendency to swing from below to above zero, then the maintenance dose of methyl thiouracil must be increased so as to maintain the *minus* metabolic rate.

The average duration of treatment was six and a half months, the longest being eight and a half months; but in no case was treatment suspended in under five months. All patients have passed the critical period of eight weeks at which recurrence is most commonly seen, and none has shown any relapse. The average total amount of methyl thiouracil used for each was thirty grammes.

It is to be noted that only three patients with toxic adenoma were treated, one being operated on subsequently and the other two being elderly and unfit for surgical treatment. The other 35 all had acute hyperplastic thyreoid glands, and in all these control of the thyreotoxicosis has been established and they are apparently normal persons except for the four patients with old-standing exophthalmos and obvious enlargement of the thyreoid gland.

Conclusions.

1. Methyl thiouracil has now superseded thiouracil in the treatment of thyreotoxicosis.
2. The minimal dose which will produce the desired effect is the safest dose.
3. Each patient is to be regarded as an individual problem, and rule-of-thumb methods are dangerous.
4. The major factor in securing any permanency of control of thyreotoxicosis is the maintenance of a zero or *minus* metabolism for a minimum period of three months before treatment is stopped.
5. The concurrent administration of a mixed vitamin preparation is necessary, and if nervous symptoms predominate added *B* group vitamin is necessary.
6. When any pronounced loss of weight has occurred, and particularly if muscle wasting is a feature, a diet rich in protein aids recovery.
7. Regular supervision of the patient is necessary over the whole period of treatment and for six months after its cessation.
8. The minimal period of treatment is five months.
9. Satisfactory results can be obtained only in cases of acute hyperplastic toxic goitre, and the earlier such patients come to treatment, the quicker is the response and the more satisfactory is the final result. Apparent cure is obtainable in 85% of such cases.
10. Gland hyperplasia and exophthalmos, of not more than four months' duration, can be relieved by the administration of *Thyroideum Siccum* during the period of maintenance dosage.
11. All patients with adenomatous thyreoid glands should be advised to submit to operation, if only as a prophylactic measure against carcinoma in later life.
12. The previous administration of iodine doubles the average time required to secure an adequate response.

Acknowledgement.

The clinical trial of methyl thiouracil in 38 cases of thyreotoxicosis was made possible by the courtesy of Messrs. Genatosan, Limited, and May and Baker, of England, and of Andrew's Laboratories, of Sydney.

THE ESTIMATION OF 2-THIOURACIL IN PLASMA AND URINE FOLLOWING ITS ADMINISTRATION IN THYREOTOXICOSIS.

By L. E. A. WRIGHT, M.Sc.,

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WITH the possible exception of radioactive isotopes of iodine (for the internal irradiation of the thyreoid gland) at present being used by Hertz and Roberts,[1] and by Evans and Chapman,[2] the most potent medical weapon as yet investigated for the alleviation of thyreotoxicosis is the antithyreoid drug, 2-thiouracil, selected by Astwood[3] after investigation of 106 chemical compounds.

A wealth of clinical data now exists on the medical use of this drug. (See Rose and McConnell,[4] Watson,[5] Nussey,[6] Williams and Clute,[7] Grainger *et alii*,[8]

McGavack *et alii*,[9] Reveno,[11] Malley,[12] Grollman,[13] Himsworth,[14] Evans and Flink,[15] Cookson,[16] and Eaton;[17] see also "Editorial" in *The Journal of the American Medical Association*,[18] "Notes and Answers" in the *British Medical Journal*,[19] and "Current Comment" in THE MEDICAL JOURNAL OF AUSTRALIA.[20]) The drug is also widely administered as a pre-operative measure (with and without iodine). (See Bartels,[21] Lahey *et alii*,[22] Clute and Williams,[23] and Moore *et alii*.[24])

It should perhaps be mentioned in passing that a small amount of statistically not very satisfactory clinical data exists on the use of some other antithyreoid drugs—namely, thiobarbital and 6-ethyl-thiouracil (Astwood[25]), allylthiourea (Hercus and Purves[26]), tetramethyl-thiourea and di-ethylthiourea (Williams[27]), methylthiouracil (Leys[28]), para-aminobenzoic acid (Berman[29]), and lately in France (where there has been no experience with 2-thiouracil), 2-aminothiazole (Perrault and Bovet[30]). Astwood and Vanderlaan[42] claimed that both 6-ethylthiouracil and 6-n-propylthiouracil had five times the activity of 2-thiouracil in man; the author has not been able to find further reports of the clinical trials of these drugs.

Hence, because of the widespread use of 2-thiouracil, an investigation of the secretion of the drug in the plasma and of its excretion in the urine during administration in thyreotoxicosis was undertaken.

Concurrently with this investigation laboratory mice were being fed on a diet containing 1·0% of the drug in the solid food, and estimations of 2-thiouracil in mouse plasma were made after the animals had been consuming the drug for different periods.

An investigation of the distribution of the drug in the erythrocytes and plasma was also carried out *in vitro*.

Experimental Investigation.

The estimation of 2-thiouracil is most satisfactorily accomplished by Grote's reagent (see Grote[31]), which was first used in this connexion by Williams, Jandorf and Kay.[32] It is a solution of sodium aquoferricyanide, which reacts with the C=S portion of the molecule to produce a soluble green-coloured complex.

Preparation of Grote's Reagent.

The method of preparation was essentially that of Williams *et alii* (*vide supra*), as follows:

Sodium nitroferricyanide (0·5 gramme) was dissolved in ten millilitres of distilled water in a small beaker at room temperature (about 20° C.), and to it was added 0·5 gramme of hydroxylamine hydrochloride, followed by 1·0 gramme of finely powdered sodium bicarbonate, when the former compounds had dissolved. The beaker was kept covered with a watch glass till all effervescence had ceased (thirty minutes), and then 0·1 millilitre of bromine was run in from a 0·1 millilitre pipette with gentle shaking. When all effervescence had again ceased (twenty minutes) the solution was filtered through a Whatman number 2 filter paper into a 25 millilitre stoppered volumetric flask, and the volume was made up with distilled water.

This solution could be kept for about two weeks in the refrigerator. It was always filtered immediately prior to use, to remove a small amount of fine, brown-coloured precipitate which separated out. For usage, the solution was diluted with five volumes of distilled water.[1] It is most important to adhere to a strict routine in the preparation of this reagent; the pH of undiluted Grote's reagent was 8·0.

Colorimetric Estimation.

As a "Lumetron" photoelectric colorimeter (model number 400) was available, this was used in preference to a visual colorimeter, because of (i) the increased sensitivity, (ii) the objectivity of method, (iii) the obviation of continual preparation of standards. In this way the unknowns could be compared with distilled water and the results read directly from a predetermined curve. The coloured complex was found to obey Beer's law in solution when the 660 millimicron filter provided with the instrument was used (this filter was also used by Williams, Jandorf and Kay); the logarithmic scale readings were plotted against the concentration for a range of 0·0 to 20·0 milligrammes *per centum* for urine and of 0·0 to 30·0 milligrammes *per centum* for plasma.

[1] Some authors have used a dilution to five volumes with distilled water; but this was found to bring the pH range of the final solutions beyond 6·8 to 7·35 (see below, discussion on the effect of altering the pH).

Estimation of the Drug in Urine.

For urine which on dilution gave an optically clear solution after filtration through a Whatman number 2 filter paper, a simple dilution procedure sufficed (after adjustment of the pH, see below); for urine from patients receiving less than 0·5 gramme per day and having an ordinary fluid intake, two millilitres were accurately measured and diluted to 25 millilitres in a ground-glass stoppered volumetric flask; for the urine of patients receiving more than 0·5 gramme per day, only one millilitre was taken unless the patient was taking an increased amount of fluid. Seven millilitres of the diluted and filtered urine were accurately measured into the container (in this case optically matched test tubes were used), and one millilitre of the diluted Grote's reagent was added, the tubes being kept in the daylight. The absorption was measured after an interval of forty minutes.

For urine which did not give an optically clear solution, a dialysis procedure was used. This would certainly not be necessary when a visual colorimeter was employed, as the opacity was not of such magnitude as to trouble the eye. The dialysis procedure was also applied to the estimation of 2-thiouracil in plasma. The simple dialysis unit was constructed by cutting off the flanged end of a half-inch test tube to a length of one and a half inches. Over the flange, which should be as narrow as possible, was tied a small piece of "Cellophane" (selected because of its ready permeability to the drug molecules—a "wrapping" quality kindly donated by the Biochemistry School, University of Melbourne, was used) about three inches square to form a small dialysis bag of a capacity of about two millilitres; the ends of the "Cellophane" were tightly bound with white cotton. One millilitre of urine at pH 6·0 approximately or of plasma was then accurately measured into the bag and the free end was fitted with a cork carrying a nine-inch length of three-sixteenth-inch glass tubing. The dialysis bag was then inserted into a test tube of a diameter of one and a quarter inches containing five millilitres of distilled water accurately measured, the free end of the glass tubing being passed through a stopper which fitted the neck of the large test tube; the levels of liquid in the bag and tube were thus able to be adjusted, the level in the bag being just above the level of liquid outside. Dialysis was carried out for twenty-six hours at 20° C. (room temperature). When the temperature was above this, the material was kept in an icebox overnight. Four millilitres of dialysate were then measured into the container and one millilitre of diluted Grote's reagent was added; after forty minutes the volume was made up to eight millilitres by the addition of three millilitres of a 1% sodium chloride solution or distilled water (both of pH 6·0 approximately).

Preparation of Standard Curves for Urine.

The standard curves for urine were prepared by adding known concentrations of the drug to pooled samples of normal urine and adjusting the mixture to pH 6·0 approximately, plotting the points obtained after the addition of Grote's reagent, both for the dilution and for dialysis procedures. The galvanometer needle was set for 100% transmission with distilled water. A series of consecutive readings was made alternatively with distilled water blank and the green thiouracil-complex solution. Four different preparations of Grote's reagent were used, and in this way a wide distribution of points was plotted; the straight lines obtained did not, of course, pass through the origin. The regression lines were not calculated.

Preparation of Standard Curve for Oxalated or Citrated Plasma.

In the preparation of the standard curve for plasma, the dialysis procedure was used. As was also reported by Paschkis *et alii*,[33] it was found impossible to repeat the procedure devised by Williams, Jandorf and Kay[32] for the estimation of thiouracil in whole blood, a procedure which made use of filtrates prepared from tryptic digests which

purported to liberate the drug from bondage with the blood proteins.

A variety of other filtrates was also prepared, both from whole blood and from plasma, to which had been added thiouracil, but without success; these included such well-known procedures as those of Folin-Wu, Hagedorn-Jensen, Somogyi-Shaffer *et cetera*.

In the literature was also described a method for expressing thiourea from serum through an ultrafilter in a closed system under pressure of nitrogen (Danowski[33]); however, the drawbacks to the use of this method appeared to be (i) that seven to ten millilitres of serum were required for one estimation, and (ii) that up to forty-eight hours were needed for the accumulation of four to five millilitres of ultrafiltrate.

Plasma (obtained by courtesy of Major R. J. Walsh, of the Red Cross Blood Transfusion Service) to which known concentrations of the drug were added was dialysed in amounts of one millilitre against five millilitres of distilled water; first one medium-sized drop of normal sulphuric acid was added to the plasma in the dialysis bag. In this way the final solutions for reading (in the colorimeter), composed of four millilitres of dialysate, of one millilitre of diluted Grote's reagent and of three millilitres of 1·0% sodium chloride solution or distilled water, generally fell within the pH range which was found optimal for colour development. It is of interest to note that plasma (without adjustment of the pH to the acid region) was found to dissolve as much as 80 milligrammes *per centum* of 2-thiouracil at 37° C. A curve (straight line) was obtained by plotting the readings of the logarithmic scale of the instrument against the drug concentrations for the range 0·0 to 30·0 milligrammes *per centum*.

Use of Whole Blood.

Owing to the hæmolysing effects of the dialysis, with the result that the highly coloured products thereof often passed through the "Cellophane", whole blood could not be used in this method.

The Effect of Altering the Hydrogen Ion Concentration.

Williams, Jandorf and Kay[32] adjusted the pH of the entire urine specimen to 8·0, and held that maximum colour was developed at pH 8·0 to 9·0 after fifteen minutes. At all time intervals from ten minutes to ninety minutes investigated at pH 8·0 by the present writer, the intensity of colour development was considerably lower than that obtained by the use of specimens adjusted to an approximate pH of 6·0, with a pH range for the final colorimetric solution of 6·8 to 7·35. In fact, adjustment of the pH to 8·0 at times caused a fall in value of as much as 30%; all pH's were determined with a glass electrode (see Table I).

Estimation of Thiouracil in Oxalated Pooled Mouse Plasma.

The anæsthetized animals were bled by cutting the large veins of the neck (after exposing the veins in the pouch formed by the retracted skin flaps), care being taken not to sever the arteries at the same time; in this way as much as 1·6 millilitres of blood could be obtained from a mouse weighing 20 to 25 grammes, as against about 0·8 millilitre obtained by heart puncture. The oxalated plasma was acidified and dialysed in the usual way, the thiouracil values being read from the curve for human plasma.

The In-Vitro Distribution of 2-Thiouracil between the Red Cells and Plasma.

Red cells which had been washed with physiological saline solution were equilibrated with equal volumes of plasma containing 40, 20 and 10 milligrammes *per centum* of the drug at 37° C., 20° C. and 10° C. (variously) for twenty-six hours; at the end of this time the cells were centrifuged off and the residual 2-thiouracil in the plasma was estimated. Cells taken from the bottom of the centrifuge cup (from the 20° C. and 10° C. experiments) were then equilibrated for a further twenty-six hours with physiological saline solution, and the amount of the drug present in the saline solution was then estimated.

The Effect of Other Substances on the Estimations.

The effects of hyperthyreoidism upon creatine metabolism need not be discussed here. Creatinine was found to give a yellow colour with Grote's reagent. The effect of added creatinine on urine estimations was examined; insufficient plasma was available for the examination of the effect on the plasma estimations. The effect of adding glutathione to urine containing the drug was also investigated, as this substance gave a green colour complex, not unlike that of 2-thiouracil itself, with Grote's reagent. Various other substances (with the C=S group) developed colour with Grote's reagent, but from practical considerations the two most likely to interfere with the estimation of 2-thiouracil were creatinine and glutathione.

Collection of Urine and Plasma.

The urine was collected under supervision; no preservatives were added. It was kept in a cool place and used immediately. Collections were arranged for 10 a.m., or as near as possible to that time. Plasma was mostly collected at 10.30 a.m. (half an hour after the 10 o'clock dose).

Results and Discussion.

Plasma.

Williams, Kay and Jandorf[34] stated that for nine different dosage levels varying from 0·2 to 1·2 grammes per day, administered to patients suffering from thyreotoxicosis, the average blood level of 2-thiouracil was about 2·5 milligrammes per 100 millilitres in nearly all cases (64 in number); they stated that in three subjects (including one with thyreotoxicosis, one normal person and one obese person) the blood cells contained about seven times as much 2-thiouracil as the plasma, and in another subject (suffering from hypertension) twice as much as the plasma. From the present in-vitro investigations there was found to be an approximately equal distribution of the drug between the cells and the plasma, and the cells and saline solution, irrespective of the temperature (the cells and plasma used were all from reputedly normal individuals). No differences could be found in the absorptive powers of the cells in the four common blood groups.

TABLE I.

The Effect of Altering the pH on the Estimation of 2-Thiouracil in Urine. (Read after an Interval of Forty Minutes.)

Patient and Date.	Volume of 24-hour Specimen in Millilitres.	pH before Addition of Grote's Reagent.	pH after Reading in Colorimeter.	Dosage of Drug per 24 Hours in Grammes.	24-hourly Excretion in Grammes.	Percentage Excretion.	Percentage Difference. (Approximate.)
D.P., 24.8.45	1,105	5·95 5·35 8·2	7·25 6·45 7·83	4×0·2	0·258 0·212 0·183	32·3 26·4 22·8	20 (fall) 30 (fall)
M.H., 29.8.45	815	6·14 5·60 7·69	7·05 6·81 7·53	2×0·2	0·128 0·127 0·111	32·0 31·8 27·8	12·5 (fall)
E.H., 2.9.45	1,130	6·05 4·50 9·65	7·30 7·0 7·9	4×0·2	0·314 0·312 0·247	39·3 38·0 30·9	30 (fall)

ILLUSTRATIONS TO THE ARTICLE BY Dr. IVAN MAXWELL, Dr. G. HUNTER AND Dr. K. SCHWARZ.

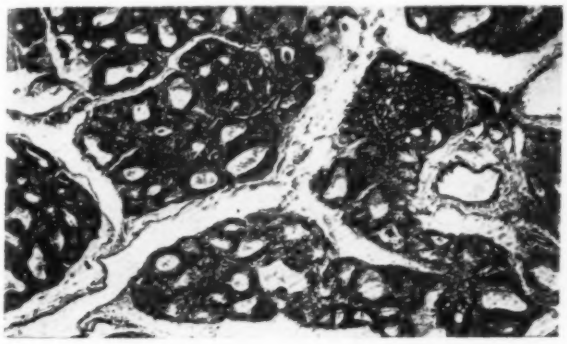

Figure XI.

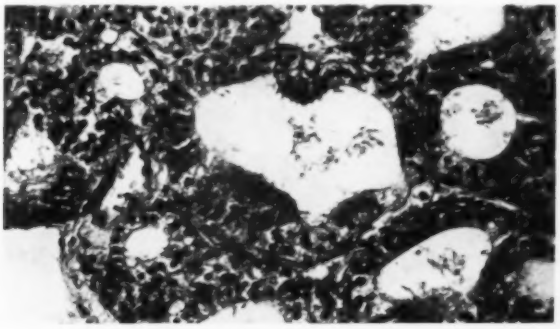

Figure XII.

Figure XIII.

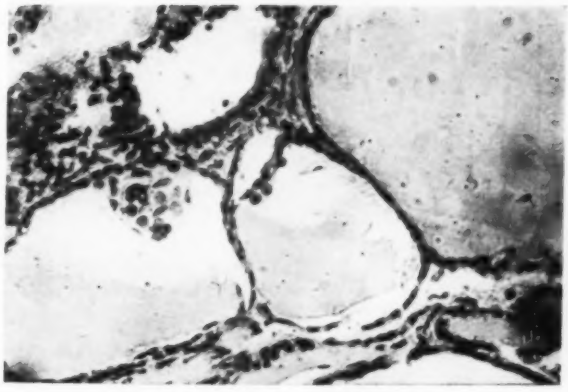

Figure XIV.

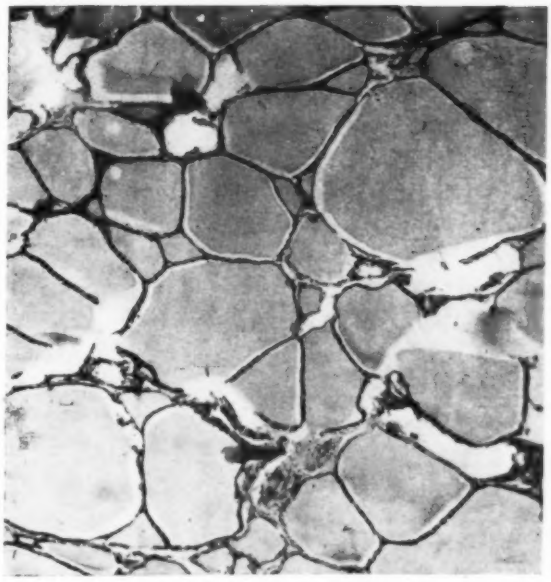

Figure XV.

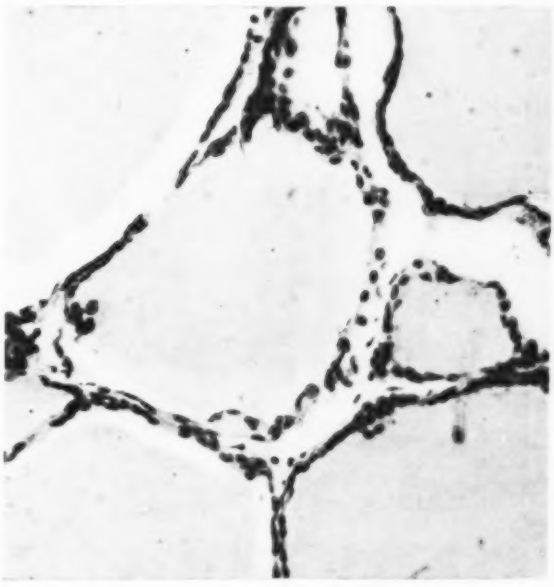

Figure XVI.

ILLUSTRATIONS TO THE ARTICLE BY Dr. H. H. HARWOOD.

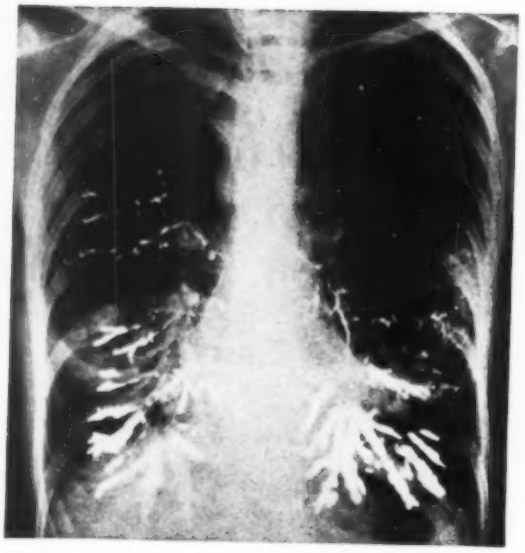

Figure I.

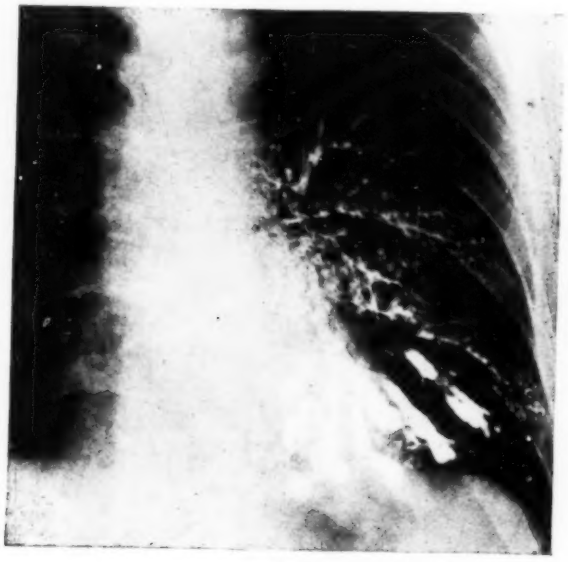

Figure II.

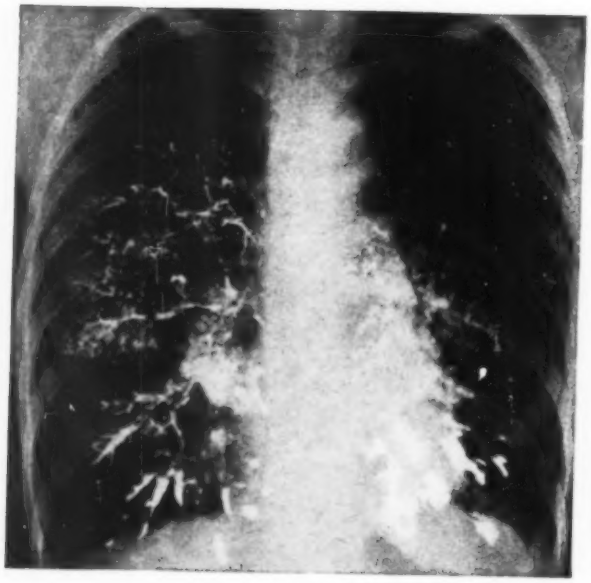

Figure III.

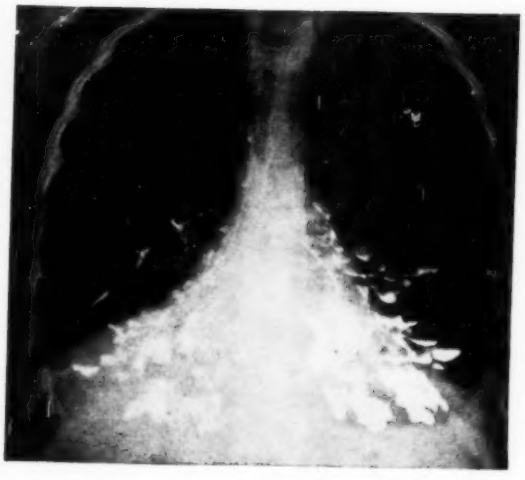

Figure V.

Paschkis *et alii*,[32] in their report appearing concurrently with these investigations, who applied Chesley's[35] procedure for the estimation of thiourea to that of 2-thiouracil, have found essentially identical concentrations in serum and laked blood which likewise indicates an equal distribution between the cellular and non-cellular elements. (It should be noted that Paschkis *et alii* also used a 660 millimicron filter.) These authors also investigated the concentrations of the drug in the serum after administration of doses of 0·2 gramme at intervals of two hours; hence because of this it was not possible to compare their findings with those described here (a four-hourly system of administration being employed).

Only very small amounts of the drug were found in the plasma of patients receiving 0·8 gramme per day; even after they had been receiving the drug for at least one week, the amounts in the plasma were only of the order of 0·3 to 0·5 milligramme *per centum*; this is in accordance with the findings of Christensen,[36] who also published the results of his investigations concurrently with this work. He examined the ultrafiltrability of thiouracil in human serum, using the Danowski[25] and the more complex Lavietes[27] ultrafiltration techniques.

Not a great deal of reliance could be placed on estimations for dosages below 0·6 to 0·8 gramme per day (particularly as the drug was not always detectable even in the plasma of those patients taking 0·6 gramme per day); had it been possible to work with smaller final volumes in the colorimeter (5·0 millilitres instead of 8·0 millilitres required by the fittings permissible under wartime import), then a reasonably accurate survey might have been achieved.

On the other hand the amounts of the drug found in pooled mouse plasma from animals receiving it in a concentration of 1·0% in the solid food were strikingly elevated (see Table II).

TABLE II.
2-Thiouracil in Pooled Mouse Plasma.

Experiment Begun.	Experiment Concluded.	Duration in Weeks.	Percentage of Drug in Food.	2% Drug in Food for 24 Hours Before Sacrifice.	Thiouracil in Plasma in Milligrammes per 100 Millitres.
7.8.44	24.10.44	11	1·0	–	3·9
7.8.44	20.11.44	15	1·0	–	9·8
7.8.44	22.11.44	15	1·0	+	7·2 7·4
7.8.44	7. 2.45	26	1·0	+	18·0
7.8.44	8. 2.45	26	1·0	+	20·7

At Sydney Hospital adult thyreotoxic patients receive approximately 1,100 grammes of solid food per day, so that 0·8 gramme of thiouracil per day represents only about 0·07% of the solid food. When the mice had reached a fairly acute hypothyreoid state, the actual intake of the drug was, of course, being reduced day to day. Also it was of interest to note that prior to the concluding stages of the experiment of some twenty-five weeks' duration, there had not been one death in the mouse colony which could be directly or indirectly attributed to the drug. This would appear to indicate that there is a species tolerance.

Urine.

Anderson,[28] using Grote's reagent, has described the urinary excretion of two patients under treatment with the drug for hyperthyreoidism. He assumed, as did the present writer, that the compound giving the reaction is unchanged thiouracil; no evidence has been advanced to the contrary. He did not, however, investigate the effect of altering the pH. Paschkis *et alii*[32] have commented upon the necessity of working on the acid side of neutrality, and adjusted the pH of their diluted urine filtrates to 6·0 prior to adding Grote's reagent; however, they did not state the pH of Grote's reagent as prepared by them, nor the pH of the solution which was read in the colorimeter.

Table III represents an investigation of the urinary excretion of 2-thiouracil of 24 thyreotoxic patients, two of whom were suffering from *diabetes mellitus* as well (E.T. and J.C.). All patients had been receiving the drug for about one week before any estimations were made; no investigations were made immediately subsequent to a change in the dosage.

It is apparent from Table III that it is impossible to predict the proportion of a particular dosage which will be excreted, as this appears to be determined by the metabolic requirements of the patient; an amount of the drug which is in accord with the needs is selectively retained. This is illustrated by the following observations.

E.H., in the group receiving four doses of 0·2 gramme per day, retained 0·480 gramme, the volume of urine being 1,130 millilitres, and 0·450 gramme when the volume of urine was 3,430 millilitres (four days later); G.C., in the group receiving three doses of 0·2 gramme per day, retained 0·300 gramme, the volume of urine excreted being 1,612 millilitres, and 0·290 gramme when the volume of urine was 1,768 millilitres; the basal metabolic rate was +12%. (Values of basal metabolic rates, descriptions of thyreoid glands and serum cholesterol values were obtained from the hospital records.)

In the group receiving five doses of 0·1 gramme per day, J.R., on March 26, 1946, retained 0·300 gramme, the volume of urine excreted being 2,351 millilitres; on April 2, 1946, she retained 0·370 gramme, the amount of urine excreted being 1,150 millilitres. This patient and E.H. (*vide supra*) together form an interesting pair for purposes of comparison. Both had hyperplastic goitres, which were removed subsequently; that of E.H. weighed 142 grammes and that of J.R. weighed 130 grammes. When the basal metabolic rate of E.H. was between +15% and +32%, between 0·350 and 0·480 gramme of 2-thiouracil was retained. When the basal metabolic rate of J.R. was between +25% and +33%, between 0·370 and 0·300 gramme was retained (as calculated from the twenty-four-hour excretion figures).

The three different estimations in the case of A.N. were also interesting. On May 1, 1946, he was receiving five doses of 0·1 gramme per day and retained 0·300 gramme, the volume of urine being 1,350 millilitres and the basal metabolic rate +24%. On June 19, 1946, when he was receiving three doses of 0·2 gramme per day, he retained 0·310 gramme, the volume of urine being 1,342 millilitres. On June 24, 1946, when he was still receiving three doses of 0·2 gramme per day, he retained only 0·110 gramme, the basal metabolic rate having fallen to +14% and the volume of urine being 1,275 millilitres.

The patient J.H., when receiving three doses of 0·1 gramme per day (see the estimations made on November 21 and November 26, 1945), retained between 0·120 and 0·140 gramme, the basal metabolic rate being +12%; later (December 10), when she was receiving two doses of 0·1 gramme per day, she still retained 0·130 gramme and the basal metabolic rate was still +12%.

J.S., receiving two doses of 0·1 gramme per day, retained 0·135 gramme on March 19, 1946, the volume of urine excreted being 1,703 millilitres, and 0·130 gramme on March 27, 1946, the volume of urine excreted having increased to 2,400 millilitres.

It will be seen from the table that in cases in which the thyreoid gland was described as considerably enlarged, the requirements of 2-thiouracil were more than in those instances in which the gland was described as only slightly enlarged or not enlarged at all. In general also, the more elevated the basal metabolic rate, the greater the 2-thiouracil requirements. There were two exceptions: T.G., receiving four doses of 0·1 gramme per day (April 17 and April 23, 1946), whose case will be discussed below, and J.S. in the same dosage group (June 19, 1946). It should be noted that both had small thyreoid glands.

McGavack *et alii*[19] observed from a small number of cases that there appeared to exist a direct relationship between the dosage of 2-thiouracil employed, the degree of elevation initially observed in the basal metabolism, and the number of days required to establish a normal level.

TABLE III.

The 24-Hourly Excretion of Thiouracil in Urine.

Patient, Sex and Date.	Volume of 24-Hour Specimen in Millilitres, and pH.	Dosage in Grammes.	Excretion in Grammes.	Percentage Excretion.	Procedure.	Remarks.	B.M.R.[1] Before Medication *per Centum*.[2]	Last B.M.R. *per Centum*.[2]	Amount of Drug Retained per 24 Hours. (Gramme.)	Description of Thyroid Gland.[2]
D.P. (F.) 23.8.45	950 pH 6·06	4×0·2	0·248 0·249	31·0 31·1	Dialysis.		+54	+37	0·550	Diffuse, enlarged smooth thyroid of regular consistency.
27.8.45	1,105 pH 5·95	4×0·2	0·258 0·251	32·3 31·4	Dialysis.		+54	+37		
E.H. (F.) 2.9.45	1,130 pH 6·05	4×0·2	0·314 0·320	39·3 40·0	Dialysis.		+57	+15	0·490 to 0·350	Subsequent thyroidectomy; thyroid weighed 142 grammes. Advanced epithelial hyperplasia; ill-defined lobules divided by fibrous septa.
6.9.45	3,430 pH 6·10	4×0·2	0·343 0·349	42·9 43·6	Dialysis.	I.F.I.[3]		+15		
12.9.45	3,123 pH 5·80	4×0·2	0·400 0·400	50·8 50·0	Dialysis.	I.F.I.		+24		
4.10.45	2,044 pH 5·92	4×0·2	0·353 0·348	44·1 43·5	Dialysis.	I.F.I.		+32		
11.10.45	4,545 pH 6·03	4×0·2	0·454 0·446	56·0 55·7	Dialysis.	I.F.I.		+20		
			0·436 0·450	54·5 53·7	Dialysis.	150 milligrammes *per centum* of creatinine.		+20		
[G.C. (M.) 1.7.46	1,612 pH 5·8	3×0·2	0·295 0·301	49·1 50·2	Dialysis.		?	+12	0·300 to 0·290	Nodular thyroid, but no enlargement.
			0·299 0·295	49·8 49·1	Dialysis.	10 milligrammes *per centum* of glutathione.		+12		
			0·298 0·296	49·6 49·3	Dialysis.	50 milligrammes *per centum* of creatinine.		+12		
		5·0 milligrammes *per centum* of thiouracil added;				4·80 milligrammes *per centum* recovered.				
8.7.46	1,768 pH 5·83	3×0·2	0·318 0·314	53·0 52·3	Dialysis.	I.F.I.	?	+12		
		5·0 milligrammes *per centum* of thiouracil added;				4·60 milligrammes *per centum* recovered.				
G.F. (F.) 30.5.46	864 pH 6·20	3×0·2	0·140 0·146	23·3 24·3	Dialysis.		+24	+23	0·460	Thyroid firm and not appreciably enlarged.
			0·144 0·144	24·0 23·9	Dilution.			+23		
			0·146 0·147	24·3 24·5	Dilution.	50 milligrammes *per centum* of creatinine.		+23		
			0·152 0·149	25·3 24·8	Dilution.	10 milligrammes *per centum* of glutathione.		+23		
22.6.46	1,960 pH 6·03	3×0·2	0·460 0·440	76·7 73·3	Dialysis.	I.F.I.	?	+23[11]	0·140	
A.N. (M.) 19.6.46	1,342 pH 5·86	3×0·2	0·288 0·298	48·0 49·7	Dilution.		+57	+24	0·310	
			0·296	49·2	Dilution.	50 milligrammes *per centum* of creatinine.		+24		
			0·287 0·292	47·8 48·7	Dialysis.			+24		
			0·277	46·2	Dialysis.	50 milligrammes *per centum* of creatinine.		+24		
24.6.46	1,275 pH 6·0	3×0·2	0·501 0·484	83·5 80·7	Dilution.		+57	+14	0·100 to 0·120	Soft uniform swelling in the neck; subsequent thyroidectomy; weight of gland removed, 75 grammes.
			0·478 0·492	79·7 82·0	Dilution.	50 milligrammes *per centum* of creatinine.		+14		
			0·486 0·500	81·0 83·3	Dilution.	10 milligrammes *per centum* of glutathione.		+14		
			0·483 0·472	80·5 78·7	Dialysis.			+14		
			0·479	79·8	Dialysis.	50 milligrammes *per centum* of creatinine.		+14		
			0·471 0·482	78·5 80·3	Dialysis.	10 milligrammes *per centum* of glutathione.		+14		
		5·0 milligrammes *per centum* of thiouracil added;				5·15 milligrammes *per centum* recovered.				

[1] Basal metabolic rate. [2] Data obtained from the hospital records. [3] Increased fluid intake.

TABLE III.—*Continued.*

The 24-Hourly Excretion of Thiouracil in Urine.—Continued.

Patient, Sex and Date.	Volume of 24-Hour Specimen in Millilitres, and pH.	Dosage in Grammes.	Excretion in Grammes.	Percentage Excretion.	Procedure.	Remarks.	B.M.R.[1] Before Medication *per Centum.*[2]	Last B.M.R. *per Centum.*[2]	Amount of Drug Retained per 24 Hours. (Gramme.)	Description of Thyreoid Gland.[2]
A.L. (M.) 15.7.46	1,223 pH 5·8	3×0·2	0·490 0·484	81·3 80·7	Dilution.		+33	+9		
			0·472 0·477	78·7 79·5	Dilution.	50 milligrammes *per centum* of creatinine.		+9	0·110 to 0·120	Primary thyreotoxicosis. Uniform bilateral enlargement of both lobes.
			0·494 0·496	82·3 82·7		10 milligrammes *per centum* of glutathione.		+9		
		5·0 milligrammes *per centum* of thiouracil added;				4·72 milligrammes *per centum* recovered.				
J.C. (F.) 9.7.46	800 pH 5·88	3×0·2	0·266 0·272	44·3 45·3	Dilution.		+25	?		
			0·266 0·264	44·3 44·0	Dilution.	50 milligrammes *per centum* of creatinine.			0·340	Moderate swelling of thyreoid gland.
			0·270 0·260	45·0 43·3	Dilution.	10 milligrammes *per centum* of glutathione.				
J.R. (F.) 26.3.46	2,351 pH 6·10	5×0·1	0·205 0·204	41·2 40·8	Dialysis.	I.F.I.[3]	?	+33		
			0·209 0·198	41·8 39·6	Dialysis.	10 milligrammes *per centum* of glutathione.		+33		Considerable uniform enlargement of thyreoid gland. Specimen on subsequent removal weighed 130 grammes. Nodule three-quarters of an inch in diameter.
2.4.46	1,150 pH 5·91	5×0·1	0·135 0·132	27·0 26·4	Dialysis.			+25	0·300 to 0·370	
			0·137 0·128	27·4 25·6	Dilution.			+25		
			0·140 0·137	28·0 27·4	Dilution.	10 milligrammes *per centum* of glutathione.		+25		
W.D. (M.) 15.4.46	1,547 pH 6·2	5×0·1	0·309 0·313	61·8 62·6	Dialysis.		+48	?		
			0·312	62·4	Dialysis.	50 milligrammes *per centum* of added creatinine.			0·200	Gland not described.
			0·3096 0·314	61·9 62·2	Dialysis.	10 milligrammes *per centum* of glutathione.				
		5·0 milligrammes *per centum* of thiouracil added;				5·18 milligrammes *per centum* recovered.				
A.N. (M.) 1.5.46	1,350 pH 6·02	5×0·1	0·204 0·2065	40·8 41·3	Dialysis.			+24	0·300	
		5·0 milligrammes *per centum* of thiouracil added;				4·81 milligrammes *per centum* recovered.				
A.H. (M.) 29.4.46	1,142 pH 6·0	5×0·1	0·252 0·248	50·4 49·8	Dilution.		+18	+10		
			0·243 0·248	48·6 49·8	Dilution.	50 milligrammes *per centum* of creatinine.		+10	0·250	
			0·242 0·250	48·4 50·0	Dilution.	10 milligrammes *per centum* of glutathione.		+10		
6.5.46	2,417 pH 6·15	5×0·1	0·308 0·310	61·6 62·4	Dialysis.		+18	+10		Hard mid-line swelling in neck below thyreoid cartilage. Thyreoidectomy: hyperplasia and involution, mostly hyperplasia. Left lobe small and atrophic. Hyperplasia of isthmus and right lobe. Measurements: 6 cm. by 3 cm. by 2·5 cm.; 5 cm. by 1·5 cm. by 2·5 cm.
			0·304 0·301	60·8 60·2	Dialysis.	50 milligrammes *per centum* of creatinine.				
			0·308 0·303	61·7 60·6	Dialysis.	10 milligrammes *per centum* of glutathione.		+10		
			0·340 0·353	68·0 70·6	Dilution.	Optically opaque.		+10	0·200 to 0·160	
			0·341 0·337	68·2 67·4	Dilution.	Optically opaque, 50 milligrammes *per centum* of creatinine.				
			0·315 0·328	63·0 65·6	Dilution.	10 milligrammes *per centum* of glutathione.				

[1] Basal metabolic rate. [2] Data obtained from the hospital records. [3] Increased fluid intake.

TABLE III.—*Continued.*

The 24-Hourly Excretion of Thiouracil in Urine.—Continued.

Patient, Sex and Date.	Volume of 24-Hour Specimen in Millilitres, and pH.	Dosage in Grammes.	Excretion in Grammes.	Percentage Excretion.	Procedure.	Remarks.	B.M.R.[1] Before Medication *per Centum*.[2]	Last B.M.R. *per Centum*.[1]	Amount of Drug Retained per 24 Hours. (Gramme.)	Description of Thyroid Gland.[2]
A.A. (F.) 22.7.46	978 pH 5·88	5×0·1	0·183 0·187	36·6 37·4	Dilution.		+35	+35	0·320	Enlarged thyroid, though not obvious; mostly in isthmus and left lobe.
			0·165 0·160	33·0 34·0	Dilution.	50 milligrammes *per centum* of creatinine.		+35		
			0·184 0·184	36·8 36·8	Dilution.	10 milligrammes *per centum* of glutathione.		+35		
A.Hn. (F.) 11.6.46	827 pH 5·81	4×0·1	0·199 0·201	49·7 50·2	Dialysis.		+30	+21	0·200	Recurrent thyreotoxicosis after previous thyreoidectomy; palpable nodular thyreoid.
S.G. (M.) 11.3.46	2,645 pH 6·10	4×0·1	0·297 0·298	74·2 74·5	Dialysis.		+42	+12	0·100	No evidence of enlargement of thyreoid.
	2,645 pH 6·10	4×0·1	0·287 0·292	71·7 73·0	Dialysis.	50 milligrammes *per centum* of creatinine.		+12	0·100 to 0·200	
		5·0 milligrammes *per centum* of thiouracil added; 5·2 milligrammes *per centum* recovered.								
18.3.46	3,012 pH 6·05	4×0·1	0·208 0·214	52·0 53·5	Dialysis.	I.F.I.[3]		+12[(11)]		
B.T. (F.) 11.4.46	1,371 pH 5·92	4×0·1	0·362 0·370	90·5 92·5	Dialysis.		+67	+23	0·040	*Diabetes mellitus* and hyperthyreoidism. Thyreoid diffusely enlarged — rather than nodular.
			0·360 0·369	90·0 92·2	Dialysis.	50 milligrammes creatinine.		+23		
			0·364	91·0	Dialysis.	10 milligrammes *per centum* of glutathione.		+23		
T.G. (F.) 17.4.46	1,665 pH 6·16	4×0·1	0·373 0·360	93·2 90·0	Dilution.		+44	+44	0·030 to 0·025	Some slight thyreoid enlargement of diffuse type.
			0·372 0·372	93·1 93·1	Dilution.	50 milligrammes *per centum* of creatinine.		+44		
			0·370 0·363	92·2 90·7	Dilution.	10 milligrammes *per centum* of glutathione.		+44		
23.4.46	2,870 pH 6·20	4×0·1	0·375	93·7	Dialysis.	I.F.I.		+46		
			0·378 0·387	94·5 96·7	Dilution.			+46		
M.H. (F.) 29.8.45	815 pH 6·14	2×0·2	0·128 0·133	32·0 33·2	Dialysis.		+64	+18	0·270	Thyreoid gland diffusely enlarged.
Je.S. (F.) 19.6.46	1,118 pH 6·11	4×0·1	0·229 0·232	57·3 58·0	Dilution.		+60	+30	0·170	Small, but definitely enlarged, diffuse firm thyreoid gland.
			0·228 0·233	57·0 58·3	Dilution.	50 milligrammes *per centum* of creatinine.		+30		
			0·222 0·220	55·5 55·0	Dialysis.			+30		
			0·227 0·221	56·8 55·3	Dialysis.	50 milligrammes *per centum* of creatinine.		+30		
M.P. (F.) 6.10.45	709 pH 5·93	3×0·1	0·127 0·123	42·3 41·0	Dialysis.		+48	+12	0·180 to 0·160	Bilaterally enlarged, smooth thyreoid.
8.10.45	890 pH 6·08	3×0·1	0·132 0·138	44·0 46·0	Dialysis.			+12		
16.10.45	949 pH 5·8	3×0·1	0·143 0·142	47·7 47·3	Dialysis.	I.F.I.		+12		
			0·141	47·0	Dialysis.	50 milligrammes *per centum* of creatinine.		+12		
			0·145 0·146	48·3 48·6	Dilution.			+12		
J.H. (M.) 5.11.45	998 pH 5·97	3×0·1	0·203 0·199	67·7 66·3	Dialysis.		?	+6	0·100 to 0·200	Slightly enlarged uniform soft thyreoid.
			0·189 0·192	63·0 64·0	Dialysis.	150 milligrammes *per centum* of creatinine.		+6		
19.11.45	1,425 pH 6·21	3×0·1	0·093 0·089	31·0 29·7	Dialysis.	2 weeks later I.F.I.		+6[(11)]		

[1] Basal metabolic rate. [2] Data obtained from the hospital records. [3] Increased fluid intake.

TABLE III.—*Continued.*

The 24-Hourly Excretion of Thiouracil in Urine.—Continued.

Patient, Sex and Date.	Volume of 24-Hour Specimen in Millilitres, and pH.	Dosage in Grammes.	Excretion in Grammes.	Percentage Excretion.	Procedure.	Remarks.	B.M.R.[1] Before Medication *per Centum*.[2]	Last B.M.R. *per Centum*.[2]	Amount of Drug Retained per 24 Hours. (Gramme.)	Description of Thyroid Gland.[2]
Je.H. (F.) 21.11.45	1,208 pH 5·9	3×0·1	0·167 0·168	55·7 56·0	Dialysis.		?	+12		
			0·162 0·169	54·0 56·3	Dilution.	50 milligrammes *per centum* of creatinine.		+12		
26.11.45	4,035 pH 6·03	3×0·1	0·178 0·172	59·3 57·3	Dialysis.	I.F.I.[3]		+12	0·140 to 0·120	Thyroid generally enlarged (smooth).
			0·166 0·170	55·3 56·3	Dialysis.	50 milligrammes *per centum* of creatinine.		+12		
E.S. (F.) 19.11.45	1,915 pH 6·04	3×0·1	0·132 0·134	44·0 44·6	Dialysis.		+73	+29	0·170	Uniformly and slightly enlarged thyroid.
		10·0 milligrammes *per centum* of thiouracil added;				9·70 milligrammes *per centum* recovered.				
J.O'H. (M.) 23.4.46	1,494 pH 6·15	3×0·1	0·174 0·179	58·0 59·7	Dialysis.		+21	+8		Thin surgical scar; right lobe absent; left lobe diffusely enlarged, firm and smooth.
			0·179 0·172	59·7 57·3	Dialysis.	45 milligrammes *per centum* of creatinine.		+8	0·120	
		5·0 milligrammes *per centum* of thiouracil added;				4·78 milligrammes *per centum* recovered.				
Je.H. (F.) 10.12.45	980 pH 6·06	2×0·1	0·073 0·075	36·5 37·5	Dialysis.	2 weeks after last estimation.		+12[11]		Smooth, generalised enlargement.
			0·070 0·071	35·0 35·5	Dialysis.	50 milligrammes *per centum* of creatinine.		+12	0·130	
J.S. (M.) 19.3.46	1,703 pH 5·83	2×0·1	0·06897 0·0653	34·5 32·7	Dilution.		+52	+14		
			0·0623 0·0648	31·2 32·4	Dilution.	50 milligrammes *per centum* of creatinine.		+14		
		5·0 milligrammes *per centum* of thiouracil added;				4·94 milligrammes *per centum* recovered.			0·135 to 0·130	Thyroid gland not enlarged.
27.3.46	2,400 pH 5·97	2×0·1	0·0697 0·0720	34·8 36·0	Dialysis.	I.F.I.	+52	−2		
			0·0699 0·0715	34·9 35·7	Dialysis.	10 milligrammes *per centum* of glutathione.		−2		
Je.S. (F.) 2.7.46	1,356 pH 6·21	2×0·1	0·143 0·148	71·5 74·0	Dilution.		+60	+21		
			0·140 0·139	70·0 69·5	Dialysis.			+21	0·060	
		5·0 milligrammes *per centum* of thiouracil added;				4·71 milligrammes *per centum* recovered.				
E.S. (F.) 3.12.45	2,254 pH 5·92	3×0·05	0·141 0·144	94·0 96·0	Dialysis.		+73	+29		
			0·138 0·140	92·0 93·3	Dialysis.	100 milligrammes *per centum* of creatinine.		+29	0·010	Uniformly and slightly enlarged thyroid gland.
R.C. (F.) 21.11.45	840 pH 5·86	3×0·05	0·131 0·133	87·3 88·7	Dialysis.		+74	?		
			0·129 0·130	86·0 86·7	Dialysis.	50 milligrammes *per centum* of creatinine.			0·020	Slight enlargement of thyroid gland (uniform).
J.S. (M.) 24.7.46	2,754 pH 6·16	0·05×2	0·0794 0·0835	39·7 41·7	Dilution.	I.F.I.	+52	+14	0·020	Thyroid gland not enlarged.

[1] Basal metabolic rate. [2] Data obtained from the hospital records. [3] Increased fluid intake.

The figures they obtained suggested to them that the action of 2-thiouracil (in thyreotoxicosis) was "quantitative" in nature. From the foregoing discussion on the retention figures of the drug at different dosage levels, at different sizes of the thyreoid and at different basal metabolic rates (corresponding as nearly as possible to the times when the estimations were made), the writer has reached a similar conclusion as to the "quantitative" action of the drug.

Owing to the fact that the drug is not so soluble in the urine as, for example, in the plasma (being roughly twice as soluble in the plasma as in the urine), then it is evident that the foregoing observations could have easily been masked at higher dosage levels. Also, if the system, as these results seem to indicate, has a definite and determinable requirement of the drug at a particular time, then because of the smaller solubility of the drug in the urine, any attack on the course of the disease involving the principles of "mass-action" is immediately fraught with risk, as the excess apparently becomes available for interaction with the myeloid elements of the bone marrow. Hence it is apparent that the drug should not be administered with restricted fluid intake; a fluid intake above the patient's normal fluid intake is preferable.

The presence of added glutathione did not affect the results, as the colour complex obtained with Grote's reagent was found to fade more rapidly (after about fifteen minutes) than that obtained with 2-thiouracil.

Creatinine at times caused a slight lowering of the logarithmic scale readings (that is, an increase in transmission); in these cases it was found that there had been a pH shift beyond the alkaline side of 7·35, due to the basic nature of creatinine (for example, see the case of A.A., July 22, 1946, receiving five doses of 0·1 gramme per day).

The patient T.G., receiving four doses of 0·1 gramme per day, was found on two occasions to be excreting 93% to 94% of the administered dose (the volumes of urine being 1,665 and 2,870 millilitres). In view of the fact that patients who received tremendous amounts of fluid nevertheless retained the amount of drug necessary for metabolic requirements, it would seem that this patient (despite an elevated basal metabolic rate of +44% to +46%) did not require an amount of 2-thiouracil which was comparable with that of thyreotoxic patients with an elevated basal metabolic rate. In spite of the administration of almost 11·0 grammes over twenty-eight days, the basal metabolic rate remained elevated. (At Sydney Hospital, basal metabolic rate determinations are made on two consecutive six-minute samples of expired air, which must give carbon dioxode absorption figures which agree to within 10% by weight, and when the pulse and respiration rates are steady and correspond for both time intervals.) This patient had received no previous iodine therapy.

Cookson[16] described a similar case, in which the basal metabolic rate rose from +40% to +51% in forty-four days, during which time the patient received 18·0 grammes of 2-thiouracil. (It should be mentioned that pregnancy was a complicating factor.) He also described another "partial failure" with the drug, in which the basal metabolic rate could not be reduced below +20%. These patients had not previously received iodine. The serum cholesterol levels rose nevertheless, as did also those of T.G. (being consecutively 87, 97, 124 and 152 milligrammes *per centum*); this indicated that there was some response to the drug after all. It is possible that the continued elevation of the basal metabolic rate of these "unresponsive" patients was due to an excess of a pituitary principle, which Collip[(60)] has termed the "specific metabolic principle"; this has been described in other animal species—namely, the guinea-pig, the rat and the rabbit—and it elevates the metabolic rate in the presence or absence of the thyreoid gland and is not mediated through the adrenals or the pituitary gland. (See also the work of Dobyns.[(61)]) Unfortunately no excretion figures for patients unresponsive to thiouracil could be found in the literature.

Summary and Conclusions.

The excretion of 2-thiouracil in the urine of 24 thyreotoxic patients receiving different dosages of the drug is discussed.

The action of 2-thiouracil in thyreotoxicosis is "quantitative" in nature.

The patient's requirements at a particular time can be found by estimating the excretion of the drug on normal fluid intake and then the excretion of the drug on increased fluid intake.

A fluid intake which is larger than the usual is recommended because of the smaller solubility of the drug in the urine, in comparison with its solubility in the plasma.

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PENICILLIN IN THE TREATMENT OF BRONCHIECTASIS.[1]

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SINCE my previous paper on the treatment of bronchiectasis by bronchoscopic lavage,[1] I have been treating some of these same patients with penicillin. It has not been possible yet to treat many, as difficulty has been experienced at times in obtaining regular supplies of the drug for these chronic conditions. However, in this paper I shall review the first twenty patients who have been given a course of treatment.

A few papers have recently been published on the use in bronchiectasis of penicillin given by injections[2][3][4] and by instillation,[3] and also in the form of penicillin mist.[5][7][8][9] My first two patients were treated by instillations alone and then later by injections and instillations. All the others have been treated by both injections and instillations. So far I have not carried out any treatment with penicillin mist.

As Olsen points out, penicillin presumably exerts its bactericidal action by contact with organisms on the bronchial mucosa. The bronchial deformities and the disturbances of bronchial function which characterize bronchiectasis are permanent changes and will not be altered by any method of treatment. Furthermore, in chronic pulmonary infections there is a varied flora, and some organisms will no doubt be present which are not sensitive to penicillin. I therefore fully explain to patients before treatment that no cure is to be expected, but that some improvement may take place.

Levine[10] states that the effect of penicillin is dependent upon the type of bacteria and upon the amount of circulation around the area affected. Stookey and others state that saccular bronchiectasis was not greatly affected by treatment. I mention this particularly, as most of my first twenty cases were of advanced saccular type, picked out because of the severity of the lesion. Sixteen of my patients had been under treatment and observation for over ten months before the use of penicillin, and six had been attending the clinic for as long as three years or more, so that in 80% of the cases we had been able to observe their reaction to treatment by bronchoscopic aspiration and lavage for a considerable time prior to treatment with penicillin. Since the treatment was completed a regular check has been kept on these patients, so that I have followed up five for twelve months, four others for nine months, six for six months and four for three months; I have thus been able to watch their reactions for some time afterwards.

My first patient had pronounced bilateral saccular bronchiectasis. For nineteen months she had been given various sulphonamides by local application at intervals during her routine bronchoscopic treatment. During this time her condition had improved considerably; she had gained six and three-quarter pounds in weight and the amount of sputum had decreased by about one-third. She started off with a bronchoscopic lavage once a week followed by instillation of 5,000 units of penicillin into the lungs. This was carried on for eleven weeks with one interval in hospital, when for two weeks she had daily instillation of penicillin, 5,000 units being put into each side, a total of 10,000 units per day. During this treatment the amount of sputum decreased by about 25%, but her weight remained about the same. She felt a little more comfortable.

At this stage she was kept in hospital for two weeks and given 15,000 units of penicillin intramuscularly every three hours, as well as 10,000 units per day by instillation into the bronchi; bronchoscopy and lavage were still carried out once a week. The amount of sputum dropped by nearly 50% and she gained one and a half pounds in weight in the fortnight and said that she felt much better in herself. Three months later she had gained seven pounds in weight, and a month later she had gained still another two and a quarter pounds. Her condition has steadily improved, and at thirteen months after the course of penicillin she has gained 12·75 pounds in weight—this as against six and three-quarter pounds for twenty-one months of treatment with aspiration and lavage. She is still coughing up about one ounce of sputum per day; but the bronchial mucosa is less congested, and she has had no hæmoptysis, whereas during the preceding twenty-one months she had numerous large and frequent small hæmoptyses.

The second patient had pronounced saccular bronchiectasis involving all lobes, with profuse foul sputum. She also was treated with the local instillation of penicillin for eleven weeks, first by the weekly instillation of 10,000 units and later by the daily instillation of the same amount. During the previous sixteen months' treatment by lavage she had gained only one pound in weight, but during the local treatment with penicillin she gained eight pounds; however, the amount of sputum remained much the same. She was then given one week's course of intramuscular injections with local instillations. As she was at a standstill three months later she was given another course of three weeks' injections and local treatment. She gained another four pounds in weight, but since then has steadily gone backwards. Now the sputum is again foul and profuse, and her weight has gone right back, while her temporary feeling of well-being has left her.

After this it was decided to treat a series of patients with a course of three weeks' treatment; injections of 15,000 units for adults and 10,000 units for children were to be given every three hours, together with daily intrabronchial instillations of 10,000 units for adults and 5,000 units for children; weekly bronchoscopic lavage was also to be carried out during the treatment. No greater strength than 500 units per millilitre has been used for local instillation since Proetz's[11] report on the action of penicillin on tracheal ciliary action. Tucker and Atkins have shown that the drug disappears from the secretions of the tracheo-bronchial tree in approximately twenty-four hours, so I have thought it advisable to give the instillations every day. The instillations are given by means of a laryngeal syringe through the cords. The transcricoid method, as was pointed out by May and Floyer, is likely to cause the patient discomfort, and the other method is usually easy in these cases.

The combination of parenteral and local treatment was considered advisable, as often some residual upper respiratory infection is present even though treatment (including operative procedures) has been carried out, and this will tend to cause some reinfection of the lung field. The rationale of this seems to have been borne out in Cases XI, XIX and XX particularly. The patient in Case XI had undergone several nasal operations, including an external ethmoidectomy, but still had some nasal discharge and headaches; these disappeared entirely after treatment. The patients in Cases XIX and XX both had some residual nasal disorder which cleared up, and in Case XX the patient's ears, which had been discharging for some time despite treatment, ceased to discharge.

[1] Read at a meeting of the Oto-Rhino-Laryngological Society of New South Wales (British Medical Association) on May 31, 1946.

Any upper respiratory infection should be dealt with first and cleared up as much as possible before treatment with penicillin is begun. This had been done in all but two of my cases (Cases XII and XIII), though in Case XII an intranasal antrostomy was performed. In Case XIII local treatment with penicillin in the antrum was given during treatment, with little response. These two patients have not done well, and both have recently undergone a double radical antrostomy. They had also missed their second week of penicillin treatment, as none was available at that time.

The most outstanding case was Case III. The patient was a girl, aged twenty years, with pronounced bilateral bronchiectasis, as shown in the X-ray film (Figure I). She had profuse sputum and was losing weight. She responded quickly to treatment and gained sixteen pounds in weight in three months, while her sputum disappeared. I have now followed her for over twelve months, and though her weight has come down again somewhat, she still has no cough and no sputum and feels extremely well. She had one cold, which cleared up quickly. At the latest lavage check the return fluid was clear except for a few specks of mucopus. The patient in Case XVI, who contracted pneumonia after appendicectomy and whose cough had persisted for twelve months when I first examined him, also has a pronounced saccular lesion at the base of the left lung, as shown in Figure II. He had no sputum during the third week of penicillin treatment and still has none at the end of six months. On lavage a few flakes can be washed out. The patient in Case VI (Figure III) has done very well, and in twelve months has gained eleven pounds in weight; before that she had gained only six pounds in over three years of bronchoscopic lavage.

It has been noticeable that these patients have a sense of well-being while undergoing treatment. Any odour present has been almost immediately relieved; but this

TABLE I.
Weights.

Case Number.	Patient's Sex.	Age in Years.	Type of Lesion.[1]	Duration of Treatment Before Penicillin Therapy. (Months.)	Weight Gain or Loss in Pounds Before Penicillin Therapy.	Weight Gain or Loss at End of Penicillin Course. (Pounds.)	Further Weight Gain or Loss in Three Months.	Further Weight Gain or Loss in Six Months.	Further Weight Gain or Loss in Nine Months.	Further Weight Gain in Twelve Months.
I	Female.	21	ss	21	+6·75	+0·25[2] +0·5	+7·5	0	+2·0	−0·5
II	Female.	28	ss	16	+1·0	+8·0[3] +2·0	+2·0	−5·5	−4·0	−0·75
III	Female	20	ss	2	−4·0	+3·5	+12·5	−1·0	−3·0	−3·5
IV	Female.	30	ss	13	−3·0	+0·5[3]				
V	Female.	9	ss	12	+2·5	+3·0	+3·5	−1·25	+3·0	0
VI	Female.	21	ss	39	+6·0	+1·5	+5·5	0	+2·0	+2·0
VII	Female.	12	ss	30	+13·0	+0·5	+3·0	+1·5	+2·0	
VIII	Female.	12	ss	37	+30·0	+5·0	+1·25	+4·75	0	
IX	Female.	10	ss	37	+22·5	+2·5	−3·0	+0·5	0	
X	Female.	31	ls	36	+19·0	−3·0	+2·5	−6·25	−0·5	
XI	Male.	28	ss	30	+8·0	−3·0	+5·5	−4·75		
XII	Male.	8	ss	3	+7·0	−4·5	+2·75	+1·0		
XIII	Female.	18	ls	2	+1·75	−1·5	−0·25	−2·0		
XIV	Male.	46	rs	42	−0·25	+4·75	−1·75	−3·5		
XV	Female.	25	ss	19	+7·75	−2·5	+2·75	−2·25		
XVI	Male.	36	ls	10	+0·5	+5·5	−5·0	+1·5		
XVII	Female.	44	rs	—	—	+2·0	−1·5			
XVIII	Female.	33	cc	21	+5·0	+0·75	0			
XIX	Male.	10	ss	36	+15·5	+4·75	−2·0			
XX	Female.	12	ss	29	+14·0	−2·0	+10·5			

[1] "ss" = saccular, both sides; "cc" = cylindrical, both sides; "rs" or "ls" = saccular, right or left side only.
[2] Local treatment only for eleven weeks.
[3] Patient died of bronchopneumonia and tuberculosis.

TABLE II.
Sputum.

Case Number.	Patient's Estimate of Sputum.		Total Amount of Sputum per Week During Penicillin Treatment. (Ounces.)			Patient's Estimate of Amount of Sputum After Course of Treatment.			
	A.[1]	B.[1]	First Week.	Second Week.	Third Week.	At Three Months.	At Six Months.	At Nine Months.	At Twelve Months.
I	+++	++	47·5[2] 25·5	36·0 14·0		+	+	+	+
II	+++	+++	50·0[3] 32·75	28·0	19·0	+	+++	+++	+++
III	+++	+++	45·5	12·0	6·0	Nil	Nil	Nil	Nil
IV[4]	+++	+++	24·0	22·5	14·5				
V	+++	+++	19·0	14·0	17·0	++	++	++	++
VI	+++	++	32·75	28·0	19·0	+	++	++	++
VII	++	+	12·0	8·5	10·0	+	+	+	
VIII	++	+	13·0	3·5	2·0	+	+	+	
IX	+++	++	11·0	6·0	5·5	+	+	+	
X	++	+	3·0	2·0	0	Nil	+	+	
XI	+++	++	17·0	9·0	4·0	+	+		
XII	++	++	?	7·0	9·0	++	++		
XIII	++	++	?	16·5	21·5	++	++		
XIV	+++	++	26·5	31·0	9·0	Nil	Nil		
XV	++	+	13·0	10·5	17·5	Nil	+		
XVI	+++	++	21·0	4·5	0	Nil	Nil		
XVII	++	++	22·5	14·5	15·5	Nil			
XVIII	++	+	7·0	5·5	2·5	Nil			
XIX	+++	++	?	7·0	6·0	+			
XX	+++	++	7·0	7·5	3·25	+			

[1] "A" = when first examined; "B" = when commencing penicillin treatment.
[2] Local treatment only for two weeks.
[3] Local treatment only for one week.
[4] Patient died.

TABLE III.

Organisms Present.

Case Number.	Before Penicillin.	After Penicillin.	Three Months Later.
I	A.[1]: Non-hæmolytic streptococci (m)[2], hæmolytic streptococci (p),[1] *Micrococcus catarrhalis* (p).[1]	A.: None.	A.: *Streptococcus viridans* (s),[1] *Micrococcus catarrhalis* (p), *Hæmophilus influenzæ* (m).
	An.[1]: Non-hæmolytic streptococci (m), hæmolytic streptococci (m), hæmolytic *Staphylococcus aureus* (m).	An.: None.	An.: Hæmolytic streptococci (s), *Streptococcus viridans* (s), *Micrococcus catarrhalis* (m).
II	A.: Non-hæmolytic streptococci (m), hæmolytic streptococci (p), *Staphylococcus aureus* (m), *Micrococcus catarrhalis* (m).	A. *Bacillus coli* (m).	A.: *Streptococcus viridans* (m), *Micrococcus catarrhalis* (s), *Hæmophilus influenzæ* (m).
	An.: Hæmolytic streptococci (m), *Staphylococcus aureus* (m).	An.: *Staphylococcus aureus* (s), *Bacillus coli* (m).	An.: Non-hæmolytic streptococci (s).
III	A.: Hæmolytic streptococci (p), *Micrococcus catarrhalis* (s).	A.: Diphtheroids (m).	A.: *Streptococcus viridans* (m), *Micrococcus catarrhalis* (p), *Hæmophilus influenzæ* (s).
	An.: Non-hæmolytic streptococci (m), *Micrococcus catarrhalis* (m).	An.: Diphtheroids (m).	An.: Non-hæmolytic streptococci (m), hæmolytic streptococci (s), hæmolytic *Staphylococcus aureus* (m).
IV	A.: Hæmolytic streptococci (m), pneumococci (s), *Micrococcus catarrhalis* (m), *Hæmophilus influenzæ* (m).	A.: None.	A.: Smear: tubercle bacilli in one month.
	An.: Non-hæmolytic streptococci (m), *Streptococcus viridans* (m).	An.: Non-hæmolytic streptococci (m).	
V	A.: Non-hæmolytic streptococci (m), *Streptococcus viridans* (m), *Micrococcus catarrhalis* (m), *Hæmophilus influenzæ* (p).	A.: Non-hæmolytic streptococci (m), *Staphylococcus aureus* (m), pneumococci (m).	A.: Pneumococci (m), *Micrococcus catarrhalis* (s), *Hæmophilus influenzæ* (m).
	An.: Non-hæmolytic streptococci (m), hæmolytic streptococci (p), *Micrococcus catarrhalis* (m).	An.: Non-hæmolytic streptococci (m), *Micrococcus catarrhalis* (m).	An.: *Micrococcus catarrhalis* (p), diphtheroids (s).
VI	A. Non-hæmolytic streptococci (m), *Staphylococcus aureus* (m), *Micrococcus catarrhalis* (m), diphtheroids (m), *Hæmophilus influenzæ* (m).	A.: *Staphylococcus aureus* (m), pneumococci (p).	A.: Non-hæmolytic streptococci (s), *Micrococcus catarrhalis* (m).
	An.: Non-hæmolytic streptococci (m), *Staphylococcus aureus* (m), pneumococci (m), *Micrococcus catarrhalis* (m), *Hæmophilus influenzæ* (m).	An.: *Staphylococcus aureus* (m), pneumococci (p).	An.: Non-hæmolytic streptococci (m).
VII	A.: Non-hæmolytic streptococci (m), hæmolytic streptococci (p), *Micrococcus catarrhalis* (m).	A.: *Staphylococcus aureus* (s), *Streptococcus viridans* (s), *Micrococcus catarrhalis* (p).	A.: *Staphylococcus aureus* (m), *Streptococcus viridans* (p), pneumococci (m), *Micrococcus catarrhalis* (p), *Hæmophilus influenzæ* (p).
	An.: Non-hæmolytic streptococci (m), hæmolytic streptococci (m).	An.: Hæmolytic streptococci (s), *Staphylococcus aureus* (m), *Streptococcus viridans* (m).	An.: Hæmolytic streptococci (s), *Staphylococcus aureus* (m), pneumococci (m).
VIII	A.: Non-hæmolytic streptococci (p), *Streptococcus viridans* (m), *Micrococcus catarrhalis* (p), *Hæmophilus influenzæ* (m).	A.: None.	A.: *Staphylococcus aureus* (m), *Hæmophilus influenzæ* (m).
	An.: Non-hæmolytic streptococci (m), pneumococci (m).	An.: *Staphylococcus aureus* (m).	An.: *Staphylococcus aureus* (m), *Micrococcus catarrhalis* (m), *Hæmophilus influenzæ* (m).
IX	A.: Non-hæmolytic streptococci (m), hæmolytic streptococci (p), *Hæmophilus influenzæ* (m).	A.: None.	A.: *Staphylococcus aureus* (m), *Micrococcus catarrhalis* (m), *Hæmophilus influenzæ* (p).
	An.: Non-hæmolytic streptococci (m). hæmolytic streptococci (p).	An.: Non-hæmolytic streptococci (s).	An.: *Staphylococcus aureus* (m), *Micrococcus catarrhalis* (m), *Hæmophilus influenzæ* (p).
X	A.: Non-hæmolytic streptococci (m), *Staphylococcus aureus* (s), *Streptococcus viridans* (m), *Micrococcus catarrhalis* (m), *Hæmophilus influenzæ* (m).	A.: None.	A.: Non-hæmolytic streptococci (s), *Staphylococcus albus* (s), pneumococci (m).
	An.: Non-hæmolytic streptococci (m), *Micrococcus catarrhalis* (m).	An.: None.	An.: Diphtheroids (s).
XI	A.: Non-hæmolytic streptococci (m), *Micrococcus catarrhalis* (m), *Hæmophilus influenzæ* (p).	A.: *Micrococcus catarrhalis* (m).	A.: Hæmolytic streptococci (m), diphtheroids (m), *Hæmophilus influenzæ* (p).
	An.: Non-hæmolytic streptococci (m).	An.: None.	An.: Hæmolytic streptococci (m), diphtheroids (m), *Hæmophilus influenzæ* (p).
XII	A.: Non-hæmolytic streptococci (m), *Micrococcus catarrhalis* (m), *Bacillus coli* (m).	A.: *Micrococcus catarrhalis* (m), *Bacillus coli* (s), *Hæmophilus influenzæ* (s).	A.: *Staphylococcus aureus* (m), *Bacillus coli* (p).
	An.: Non-hæmolytic streptococci (m), hæmolytic streptococcus (s), *Bacillus coli* (m).	An.: Non-hæmolytic streptococci (m), *Bacillus coli* (m).	An.: *Staphylococcus aureus* (m), pneumococci (s), *Bacillus coli* (s).
XIII	A.: Non-hæmolytic streptococci (m), *Streptococcus viridans* (m), *Bacillus Friedländer* (m).	A.: *Staphylococcus albus* (s).	A.: *Staphylococcus aureus* (m), *Hæmophilus influenzæ* (p).
	An.: Hæmolytic streptococci (m), *Streptococcus viridans* (m).	An.: Non-hæmolytic streptococci (s), *Staphylococcus albus* (m).	An.: *Staphylococcus aureus* (m), *Bacillus coli* (m), *Hæmophilus influenzæ* (m).
XIV	A.: Non-hæmolytic streptococci (m), *Bacillus Friedländer* (m).	A.: None.	A.: None.
	An.: Non-hæmolytic streptococci (p), *Micrococcus catarrhalis* (m).	An.: Pneumococci (s), diphtheroids (m).	An.: None.

[1] "A" = aerobic culture; "An" = anaerobic culture; "p" = profuse; "m" = moderate; "s" = scanty; "vs" = very scanty.

TABLE IIII.—*Continued.*
Organisms Present.—Continued.

Case Number.	Before Penicillin.	After Penicillin.	Three Months Later.
XV	A.[1]: Non-hæmolytic streptococci (m), *Bacillus Friedländer* (m).	A.: None.	A.: Non-hæmolytic streptococci (m), *Micrococcus catarrhalis* (s), diphtheroids (s), *Hæmophilus influenzæ* (m).
	An.[1]: Non-hæmolytic streptococci (s), pneumococci (s).	An.: None.	An.: Non-hæmolytic streptococci (m), *Staphylococcus aureus* (m), *Micrococcus catarrhalis* (m).
XVI	A.: *Staphylococcus aureus* (s), pneumococci (m), *Hæmophilus influenzæ* (s).	A.: *Staphylococcus aureus* (s), *Streptococcus viridans* (s).	A.: *Bacillus coli* (s).
	An.: Hæmolytic *Staphylococcus aureus* (m), Pneumococci (m), *Bacillus coli* (m), *Hæmophilus influenzæ* (m).	An.: Non-hæmolytic streptococcus (m), hæmolytic *Staphylococcus aureus* (m).	An.: *Bacillus coli* (s).
XVII	A.: *Streptococcus viridans* (m), pneumococci (m).	A.: *Staphylococcus aureus* (s).	A.: Non-hæmolytic streptococcus (vs).
	An.: *Streptococcus viridans* (m), pneumococci (m).	An.: *Staphylococcus aureus* (s).	An.: Non-hæmolytic streptococci (vs).
XVIII	A.: Hæmolytic streptococci (s), *Staphylococcus aureus* (m), *Bacillus coli* (m).	A.: *Bacillus coli* (p).	A.: Diphtheroids (s), *Hæmophilus influenzæ* (p).
	An.: Non-hæmolytic streptococci (m), hæmolytic streptococci (s).	An.: *Bacillus coli* (p).	An.: Diphtheroids (s), *Hæmophilus influenzæ* (s).
XIX	A.: *Staphylococcus aureus* (s), *Streptococcus viridans* (m), *Hæmophilus influenzæ* (m).	A.: *Bacillus coli* (m).	A.: *Staphylococcus aureus* (s), *Bacillus coli* (p), *Hæmophilus influenzæ* (m).
	An.: Non-hæmolytic streptococci (m), *Staphylococcus aureus* (m).	An.: *Bacillus coli* (m).	An.: Non-hæmolytic streptococci (m), *Bacillus coli* (p), *Hæmophilus influenzæ* (m).
XX	A.: Non-hæmolytic streptococci (m), hæmolytic streptococci (p), *Bacillus coli* (s).	A.: None.	A.: Hæmolytic streptococci (m), *Micrococcus catarrhalis* (m), *Hæmophilus influenzæ* (m).
	An.: Non-hæmolytic streptococci (m) hæmolytic streptococci (m).	An.: *Bacillus coli* (s).	An.: Hæmolytic streptococci (p), *Hæmophilus influenzæ* (m).

[1] "A" = aerobic culture; "An" = anaerobic culture; "p" = profuse; "m" = moderate; "s" = scanty; "vs" = very scanty.

returned shortly in Case II. I found that the sputum generally became more sticky, contrary to other writers' reports, but no viscosity tests have been made.

In view of Moehlig's[12] suggestions about the pituitary in relation to pulmonary osteoarthropathy, it is of interest to note that in Case VIII the condition of onychauxis was pronounced in the thumb and first finger-nails and in the toe-nails. After treatment with penicillin this condition commenced to clear up, and the patient's nails are now normal. Figure IV shows the thumb-nails, photographed

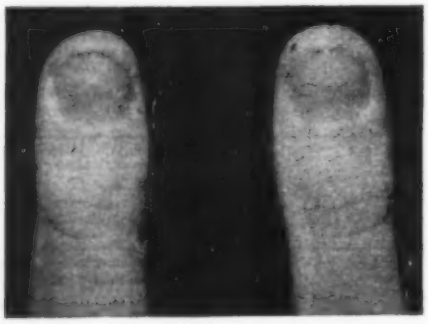

FIGURE IV.

when the normal nail had grown about half-way up. In Case XX the toe-nails are now also showing similar improvement. I have seen this occur also in a case, not in this series, in which alteration in all the nails was pronounced. No change was noted after lobectomy, but later during pregnancy the finger-nails and toe-nails gradually returned to normal. The patient in Case V, a small, pigeon-chested girl with much sputum, who had remained the same height for a considerable time, grew three and a half inches in height in five months after penicillin treatment; she also gained eight and a quarter pounds in weight in twelve months, whereas in the previous twelve months she had gained only two and a half pounds. Her X-ray film is shown in Figure V; as will be noted, she had gross saccular lesions at the bases of both lungs.

A study of the weights in Table I will show the variations at intervals of three months after treatment. It will be seen that sixteen of the twenty patients gained in weight during treatment, while twelve had continued to gain in weight at the end of three months. As compared with the rate of increase in weight prior to treatment, it is noted that eleven gained in weight at a greater rate after treatment.

Table II shows the amount of sputum as estimated by the patient before and after treatment and measured while in hospital during treatment. The total amount of sputum expectorated per week while the patient was in hospital is measured only for the six days between bronchoscopic lavage, as the patient will have some washed out and not measured during this procedure. It will be seen that thirteen had had some reduction of the amount of sputum during treatment before their course of penicillin, but the eighteen had less sputum after this treatment. It will also be noted that there was a diminution in the amount of sputum during each week of treatment in seventeen cases. The amount dropped, on the average, by 25% in the second week to 50% in the third week. Some patients had no sputum at the end of treatment, while some were still free from sputum at the end of three months or even longer.

As far as the bacteriology is concerned, the usual run of organisms was found. The specimens were all taken from the bronchi and have been examined regularly over some considerable time. It will be seen by Table III that the organisms present in the cultures obtained at the end of the period of injections are greatly diminished. While in some cases no organisms can be grown on attempted culture, in others only some non-sensitive organisms such as *Bacillus coli communis* or *Hæmophilus influenzæ* are present. After three months it will be seen that various organisms, either of the original or of fresh varieties, appear in the sputum again. However, on the whole the organisms do not appear to be so profuse as formerly. At three months in several no cultures could

be obtained, or only non-sensitive organisms were present, and in Case XIV no organisms could be grown at six months. However, after three months the flora appears gradually to increase, but not at such a rate as might have been expected. Table IV shows the number of cases in which sputum was present containing specified organisms at given periods. It will be noted that the staphylococci seem to reappear more readily than the streptococci; but it will be seen by Table III that they have appeared later in some cases in which they had not been present before.

TABLE IV.

Number of Cases in which Each Type of Organism was Isolated.[1]

Organism.	Before Treatment.	After Treatment.	After Three Months.
Aerobic culture.			
Non-hæmolytic streptococci	14	1	4
Hæmolytic streptococci	7	0	2
Streptococcus viridans	6	2	4
Micrococcus catarrhalis	10	3	9
Pneumococci	2	2	3
Staphylococcus aureus	6	5	6
Staphylococcus albus	0	1	1
Diphtheroids	1	1	3
Hæmophilus influenzæ	8	1	13
Bacillus coli	3	4	3
Bacillus Friedländer	3	0	0
Anaerobic culture.			
Non-hæmolytic streptococci	15	5	6
Hæmolytic streptococci	9	1	5
Streptococcus viridans	2	1	1
Micrococcus catarrhalis	5	1	5
Pneumococci	5	2	2
Staphylococcus aureus	5	5	7
Staphylococcus albus	0	1	0
Diphtheroids	0	2	4
Hæmophilus influenzæ	2	0	7
Bacillus coli	2	5	4

[1] Case IV has not been included in this table.

Routine blood counts have been made and sedimentation rates have been estimated during treatment and observation of the patient; but nothing of material interest was revealed by them, though it was noticed that in some cases there was a tendency for the sedimentation rate to be lowered.

Conclusion.

A general *résumé* of the condition of each patient at the present time is given, together with the patient's comments (Table V). From it we see that fifteen of the patients have felt improved after treatment, the condition of four has remained about the same after a temporary improvement, and one patient died from bronchopneumonia complicated by tuberculosis which had not been evident previously. While it is thought that these patients have been generally benefited by treatment, it is still open to question how long this improvement will last. Only by careful follow-up over a long period can this be efficiently checked.

It would appear that we can improve the condition of the patient more rapidly with the use of penicillin together with bronchoscopic aspiration and lavage than is possible with aspiration and lavage alone. Therefore I would suggest the routine of treating any sinus condition first, and then giving a course of penicillin and brochoscopic treatment as outlined above. During this treatment the patient still continues with postural drainage and inhalations.

The cases included in this series are all well advanced, and it is possible that if the treatment was given in a series of cases in which the lesions were less severe, the results would be an improvement on those quoted above.

Acknowledgement.

I wish to thank the staff of the Fairfax Institute of Pathology at the Royal Prince Alfred Hospital for their close cooperation and help in the bacteriological investigations in these cases.

TABLE V.

Progress.

Case Number.	Condition of Patient.	Patient's Comments.
I	Sputum lessened, then increased a little after three months. Looks better altogether. (After twelve months.)	"Feel better than I have ever felt. Have had no hæmoptysis for twelve months; before that, very frequently."
II	Much improved for very short time, then quickly returned to old condition. (After twelve months.)	"Felt very well for a couple of months, but have gone right back again now."
III	Has never looked back since treatment. On last lavage few flecks of mucopus. (After twelve months.)	"Feeling simply marvellously well, have had no cough at all and feel as if I had been cured."
IV	Died of bronchopneumonia six weeks after treatment. Two weeks earlier sputum contained tubercle bacilli, though 17 previous specimens from bronchi did not. X-ray examination revealed no signs of tuberculosis.	
V	Still a good deal of sputum. Looks much better, can do more and has increased in weight and height, both being previously stationary. (After twelve months.)	"Feel a great deal better, and have gone to school for the first time." Mother very pleased with progress, and says "eating much better".
VI	Had a few colds, but generally appears much better. Colour good and weight increased. (After twelve months.)	"I feel, very definitely, a great deal better since having penicillin. Am eating and sleeping better."
VII	Condition much about the same as before treatment. No definite improvement. (After nine months.)	"Feel very much the same as I did before having penicillin."
VIII	Has been much better, less sputum, chest clearer. Nails improved and looks better. (After nine months.)	"Feel extremely well and have no night cough now. Am eating very much better."
IX	Appears better since having treatment, but not a great deal of improvement. (After nine months.)	"Felt very much better for about three months and then seem to have remained at that."
X	Was very well for three months but went to live at Cobar and has steadily gone back since then. (After nine months.)	"Felt very much better till I went to Cobar. Sputum and cough were both less after treatment."
XI	Improved after treatment. Much less sputum and residual nasal condition quite settled down, leaving nose clear. (After six months.)	"Feel very much better since having penicillin. Nose is quite clear now and only coughing up a little mucus."
XII	Not a great deal of improvement but has since had double radical antrostomy done. (After six months.)	"Feel well but am still coughing a lot."
XIII	Improved for a few weeks and then went back. Was not cooperative and has since had double radical antrostomy done. (After six months.)	"Felt a little better for a short while after treatment."
XIV	Has improved considerably. There are now only a few flakes of mucopus on lavage. Looks better. Had one slight hæmoptysis recently. They were quite frequent before. (After six months.)	"Feel very much better since having penicillin. Still have a slight cough but practically no sputum."
XV	Has improved. Practically no mucopus on lavage. Weight has remained about the same. (After six months.)	"Feel better since having treatment and am not coughing so much."
XVI	Condition has cleared up considerably. Return on lavage clear now. (After six months.)	"Feel very much better since having treatment. No cough at all now."
XVII	Has improved considerably and her sputum is reduced. Lavage return is now practically clear. (After three months.)	"Feel very much better than I have done for a very long time. I have no cough at all now."
XVIII	Looks much better and lavage return is now practically clear. (After three months.)	"Feel very definitely better since having penicillin. I am not coughing very much at all and have no sputum now."
XIX	Seems much improved. Still has some sputum, but residual nose condition has improved. (After three months.)	"Feeling much better since having treatment." Father says he is much brighter altogether.
XX	Looks well. Slight nasal discharge has stopped and ears have ceased to discharge. (After three months.)	"Feeling very well since having penicillin."

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Reviews.

HYPERTONY AND THE PREVENTION OF DISEASE.

IT is very difficult to say whether Dr. Harris's book is founded on a solid mass of facts or on a number of imperfectly digested studies fitted in to square with a set of preconceived ideas.[1]

To Dr. Harris calcium is the villain of the high blood pressure tragedy, and he sets out to prove it in a number of isolated studies. Most biochemists will tell us that the blood calcium level is very constant—that in general it is very difficult to alter it by taking in more calcium. On what this regulating machinery may depend there seems at present little agreement—certainly in the absence of vitamin *D* the body will take up less calcium to a dangerous degree and in certain areas it is known that the body calcium does diminish. With this is bound up too the problem of the relations of bone calcium—ionized calcium—phosphates and phosphatase. To these Dr. Harris pays little attention.

It is interesting that actually it has been held that in western Queensland a calcium deficiency is very common. Some practitioners working in this area have been led to believe that the deficiency is related to the greater frequency of eclampsia and high blood pressure among pregnant women in these areas. This deficiency they are able to correct by giving increased supplies of calcium phosphate.

Dr. Harris, too, makes a very bitter attack on the British Food Ministry's plan of adding calcium to the standard loaf, though it has been quite definitely stated from many experiments that the adult British diet today is lacking in calcium. But this is based on the work of Widdowson and McCance, of whom Dr. Harris will have nothing.

But although he is very dogmatic on the subject of calcium and its evil effects, it would be unfair to judge Dr. Harris purely by this part of his book. There are accounts of experiments which, to put it bluntly, one would like to see confirmed by other workers, especially the effect on blood pressure in rabbits given high or low calcium feeding. Actually, too, there seems a little uncertainty whether cholesterol may not be a factor as well as protein and calcium. Those who believe that high cholesterol intake is a cause of raised blood pressure have great difficulty in explaining why this disease is practically unknown among the Eskimos. This Dr. Harris explains by their low consumption of fat. The picture of Eskimo life and diet given by de Poncins in "Kabloona" does not support his statement.

But in addition to this very controversial matter there are other chapters which are of a considerable degree of interest. One of these deals with the routine examination of a number of normal individuals. We all know how valuable these regular checks have become, but at the same time it is very doubtful how much we can arrest the march of arteriosclerosis once it has begun. Dr. Harris is quite certain; he would cut down protein and calcium and get the patient's weight down. As to this last point, he states that as weight goes down so does blood pressure fall. It is simple clinical experience that too often the advance of blood pressure is accompanied by wasting, and that some of the worst cases of hypertension occur in meagre men and women.

On the other hand the combination of excessive weight and raised blood pressure is bad, so much so that in life insurance it has been suggested that the final loading should be based on a multiplying of weight and blood pressure loading rather than on an addition. But in all probability this increased liability to disaster is not so much of biochemical origin, but arises because every extra pound the arteriosclerotic heart has to carry contributes to its fatigue.

In this respect, too, it must be remembered that estimation of the size of the heart must be very cautiously made in stout people. At least one of the things learned from mass fluorography is the fact that the old simple methods of determining heart size are misleading, and often what appears to be a grossly enlarged or a hanging drop heart is not evidence of the disease, but merely part of the body make-up. A similar danger is present in accepting a left axis deviation as definite evidence of cardiac enlargement, especially of the left ventricle.

Taking the whole book, it is provocative and calls for consideration by other investigators as to the truth or otherwise of Dr. Harris's claims. One irritating feature must be mentioned—there is no index.

[1] "Studies in Hypertony and the Prevention of Disease", by I. Harris, M.D., in cooperation with J. T. Ireland, B.Sc., A.I.C., G. V. James, M.Sc., A.I.C., Edward Cronin Lowe, M.B.E., M.B., B.S., and C. E. Vernon, M.Sc., A.I.C.; 1946. Bristol: John Wright and Sons Limited; London: Simpkin Marshall (1941) Limited. 7¼" x 5", pp. 120, with illustrations. Price: 12s. 6d.

AN ATLAS OF SKIN DISEASES.

DR. HENRY C. G. SEMON has issued a third edition of his "Atlas of the Commoner Skin Diseases".[1] This edition contains 139 coloured plates as compared with 120 plates in the second edition. Besides this, two of the plates of the second edition have been replaced by better examples of the disease they represent. It is to be pointed out that the illustrations are the result of colour photography of the diseases as existing in the living subject and that the whole production is purely British. Among the new illustrations are some of "Some Less Common Skin Diseases" including two small plates of leprosy in any early stage. These are, by reason of the early stage, less convincing to those unaccustomed to seeing all varieties of leprous manifestations than the great majority of the plates, which are excellent. The author in the second edition pointed out that it was impossible by any artificial process to reproduce exactly the colours represented in life by the various diseases. Always remembering that the colour or combinations of colour occurring in life vary considerably in the lesions of many diseases in different patients, we would insist that the great majority of Semon's illustrations approach the real as nearly as one example in life approaches in colour and line many other examples of the disease. In this matter the oft-mistaken *pityriasis rosea* (plate LXXX) and *lichen planus* (plate LX) are two of the best (among many excellent) examples.

The text attached to each plate is remarkable for its conciseness and the amount of information (ætiology, diagnosis and even treatment) contained therein. In his preface to the third edition Dr. Semon quite rightly insists that criticism to the effect that his description of treatment is too brief is unjust, and that an atlas cannot take the place of a regular textbook. Such books of illustrations are invaluable to build up and refresh the visual memory, and to enable a practitioner in general practice, by recalling one or more of the illustrations, to make at least a provisional diagnosis. The Semon atlas is also very useful to the practising dermatologist for reference, and, as the author expresses it, as *"aides-mémoire"*.

Beyond all doubt Semon's atlas (third edition) is something without which no general practitioner or dermatologist can afford to go. We regard it as one of the most valuable volumes for all medical practitioners since skin lesions accompany so many internal diseases.

[1] "An Atlas of the Commoner Skin Diseases, with 139 Plates Reproduced by Direct Colour Photography from the Living Subject", by Henry C. G. Semon, M.A., D.M. (Oxon.), F.R.C.P. (London), photography under the direction of Arnold Morits, B.A., M.B., B.C. (Cantab.); Third Edition; 1946. Bristol: John Wright and Sons Limited; London: Simpkin Marshall (1941) Limited. 9¾" x 7¼", pp. 352, with many illustrations. Price: 50s.

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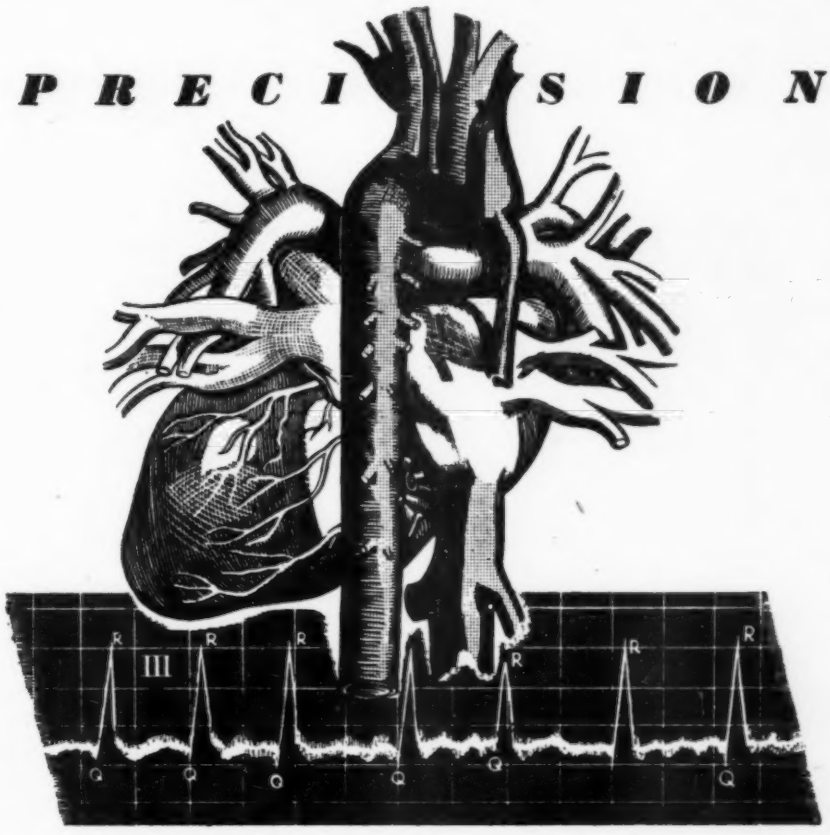

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UNIFICATION OF DRUG STANDARDS.

RECEIPT of a copy of the *Bulletin of the Health Organisation* of the League of Nations[1] redirects attention to an unobtrusive, but by no means unimportant, activity of this body. This issue, devoted to the international unification of drugs, deals extensively with biological standardization in general, together with international standards for immunological products, drugs, hormones and vitamins. It includes also an interim report of the Technical Committee of Pharmacopœial Experts on the subject of the unification of pharmacopœias.

Whatever may be the outcome of individual reflections on the intensely national character of science as applied to the destruction of human life and property, it is accepted without challenge that its application to the promotion of health and to the saving of life should be international. As a natural corollary to such an acceptance any efforts aimed at the unification and standardization of the medicinal agents adapted to this purpose merit the widest support and approbation.

In an opening paper, Dr. R. Gautier, secretary to the Permanent Commission on Biological Standardization, reviews the activity of his section over a decade, during which time the number of internationally standardized preparations has been increased to a total of thirty-five. While insisting on the greatest possible accuracy in the definition of biological standards and their interpretation in terms of international units, Dr. Gautier would allow to individual experts considerable discretion in the adoption of biological methods of assay. He maintains that an imposed and arbitrary uniformity of method and detail would tend to stereotype knowledge and to hinder progress, while freedom of choice is an incentive to research into means of improving existing methods. In addition to this, each worker is likely to make the most accurate assays when using methods with which experience and opportunity have made him familiar. There will necessarily be some divergence of results sequent on this allowed freedom of choice, but probably no more than is inherent in any biological method when one realizes the relative inaccuracy of the biological end-point as compared with that of a chemical titration. In any case the degree of variation is unlikely to be such as to have any appreciable effect on practical therapeutic application. Despite these observations the committee publishes intimate details of methods which in the hands of their experts have given most satisfactory and uniform results. Dr. Gautier notes in this connexion that biological method must be regarded as an expedient to be replaced by chemical assay as soon as sufficiently accurate and specific methods can be determined. When such is possible, as has occurred with many hormones and vitamins, active therapeutic principles will in many cases become available in chemically pure form and will be administered in dosage by weight rather than in terms of units.

In 1935 the commission had established international standards for 25 drugs, including sera, vitamins, hormones and others; but while these had been officially adopted and legally sanctioned in many countries, the number of cooperative countries was not sufficient to satisfy the commission's ultimate aim of assuring a world-wide uniformity. To this end an intergovernmental conference attended by representatives of 24 countries was held under the chairmanship of Dr. Th. Madsen. Its first recommendation, advocating the compulsory use of international standards and of the units expressing their activity, found such support that within eighteen months 36 countries had officially adopted them, and this number has since increased. For economy of operation and distribution of the standards it was recommended that each country should set up an official laboratory with a specialized staff to hold and store under optimum conditions the necessary stock of international standards. Such a centre should also reproduce international standards so as to provide national standards of identical activity and to distribute the latter to manufacturers and research workers of the country. With this set-up, the task of the two established central laboratories—the "Statens Serum Institut" of Copenhagen and the National Institute for Medical Research at Hampstead—which stock the various international standards on behalf of the Health Organisation, would be greatly eased in that they would have to assure periodical distribution of these standards to one agency only in each country. As an outcome of this conference, 19 new countries in 1936 agreed to make the use of international standard units compulsory, while 39 national centres were set up, and these standards have now been introduced as the basis of appropriate assays in most national pharmacopœias recently drawn up or revised.

Maintenance of the principle of free distribution of stocks of these standards was agreed to by the conference, and this has been effected by the Health Organisation—the necesary credits having been regularly voted year after year, despite curtailments in the League's budget in other directions.

An interesting situation examined by the conference was that arising in a specific case where an important drug

[1] "Bulletin of the Health Organisation", League of Nations, Volume XII, No. 1: Biological Standardisation, Unification of Pharmacopœias; 1945/46. Geneva: League of Nations; Sydney: H. A. Goddard Limited. 9½" × 6¼", pp. 179. Price: 6s. 3d.

was protected in its manufacture and assay by patent rights. This raised a question of principle on which the attitude of the different countries was not concordant, namely, whether the granting of patents covering the manufacture and assay of a drug could be considered as legitimate if scientific research and the struggle against disease would be hampered thereby.

In concluding his paper Dr. Gautier pays special tribute to two world-renowned scientists, who for the last twenty-five years have been pioneers in biological standardization—Dr. Th. Madsen and Sir Henry Dale. He expresses also the commission's gratitude to Sir Percival Hartley, who has given to the organization the benefit of a vast knowledge of biochemical processes and of an impeccable technique; and to Dr. Johs. Ipsen, whose capacity for investigation and whose knowledge of biostatistical methods have complemented the activities of his colleagues.

A complete bibliography of the papers published by the Health Organisation on biological methods and standards is itself a useful and impressive document, testifying to the wide scientific activities of this body. Two papers by Sir Percival Hartley, Director of Biological Standards, National Institute of Medical Research, London, describe the extraordinary measures and precautions taken to safeguard the stocks of international standards and units during the late war, and the technique to be followed for reproducing them if necessary. These notes will prove of greatest value to control centres desirous of setting up standard preparations for national requirements. In relation to the war casualties suffered by the organization one cannot but note, with some national pride, the activity of the Hampshire Institute. When in 1940 Denmark was invaded, the Copenhagen Institute was unable to transmit its standard preparations to other countries. At the request of the Health Organisation, the Medical Research Council of Great Britain, to which the Hampshire Institute belongs, undertook and continued this international service.

As a corollary to the adoption of international standards for drugs, it is but a short step to the setting up of an international pharmacopœia. The desirability of establishing uniformity among national pharmacopœias has long been recognized and the obvious value of such action need hardly be stressed. A common system of nomenclature, such that the same name should represent in all countries a drug of the same strength and composition, is an urgent need. Apart from being a potential danger to travellers who may require to have the same prescription dispensed in different countries, the confusion arising from the retention of different national standards for a widely used drug bearing a common name must restrict the free exchange and spread of clinical observation and of pharmaceutical information. Uniformity of standards, on the other hand, would stimulate economy of production and would facilitate international commerce. On this theme Dr. C. H. Hampshire, Chairman of the Technical Commission of Pharmacopœial Experts and, incidentally, Secretary of the British Pharmacopœial Commission, contributes an historical review of the progress to date. Early attempts to set up an international pharmacopœia were made in the years between 1874 and 1902. In 1902 a conference called by various governments drew up the First International Agreement for the Unification of the Formulæ of Potent Drugs, and ratification of this in 1906 had a considerable influence on national pharmacopœias subsequently published. Further conferences between 1925 and 1929 were productive of a Second International Agreement which carried the objective still further by mutual agreement as to general principles involved in nomenclature, in preparation of galenicals and their dosage and in certain biological tests. Among other advances was the decision designed to provide a permanent secretariat to coordinate the work of national pharmacopœial commissions. As an outcome of this the Health Organisation of the League of Nations set up in 1937 a technical commission of pharmacopœial experts having a wide and authoritative representation and charged with the duty of drafting further specific propositions towards the unification of pharmacopœias. Though the task was partly in abeyance during the war years, much ground has been covered and a report is published tabulating part of the work already accomplished and indicating the lines along which future work should proceed.

Included in this report are sound general rules relating to nomenclature and to the preparation and strengths of galenicals. A table of usual and maximal doses is published—be it noted, in the metric system only. With regard to dosage it is ruled that while the physician has the right to prescribe doses larger than the maximal doses quoted, the pharmacist must not dispense quantities in excess of these without express instructions from the prescriber. To the pharmacist is conceded the right to refuse to dispense doses exceeding the maxima, because in many countries the law makes the dispenser responsible for accidents due to overdosage. A large number of draft monographs—models of clarity and definition—are presented, together with an extensive list of drugs still under study for inclusion in an international pharmacopœia.

All the operations covered by the Health Organisation in its several branches indicate a wholesome and vigorous cooperation between representatives of many nations, and the teamwork, carried out in the true spirit of the League of Nations, is an example, in a limited field, of what international collaboration can achieve. Much has been done, but the work thus started and reviewed in the *Bulletin of the Health Organisation* has become an international necessity, and whatever new organization may be developed to absorb and expand the activities of the present League of Nations, it is to be hoped that ample provision will be made for an unchecked continuity of this valuable work.

Current Comment.

PREMATURE PUBLICATION IN VITAMIN RESEARCH.

HASTE in publishing the results of scientific investigation before such investigation has been carried to a satisfactory approach to completeness is a serious disability arising largely from rivalry, otherwise healthy, between research schools. The rush to secure the honour of priority has led to some very unfinished work and some unfortunate conclusions which have afterwards required a good deal of explaining. It has happened more than once that an American investigator has described a technique which he claimed to be 100% perfect, but has shortly

afterwards published a modification which would give more accurate results. Vitamin investigation has been particularly prolific in the announcement of uncritical experimentation and often in wholly wrong conclusions. When the prize for high content of ascorbic acid was given to various hips and haws, then to parsley and then to pickled walnut, there came the disconcerting discovery that the method of quantitative determination was faulty in that it included substances which were not really ascorbic acid and were incapable of acting in place of this vitamin. The latest instance of the correction of faulty experimentation is contained in a recent issue of *The Biochemical Journal*. Mincing a raw vegetable food was announced a few years ago to produce a considerable reduction in the vitamin *C* content; indeed a refinement in this revelation was that mincing made with a stainless steel implement caused less destruction of the vitamin than mincing with ordinary steel. The theory underlying this conclusion, and it had a basis of genuine reality, was that the very labile vitamin *C* is attacked by oxidases liberated from the crushed vegetable tissue. Then came the disturbing announcement that ordinary mastication in the mouth also reduces the vitamin *C* concentration of fresh vegetables.[1] This took place at a time when physiologists were endeavouring to find out why, in cases of occluded œsophagus, masticated food when admitted to the stomach through a gastric fistula was better digested and assimilated than the same type of food minced by a machine. The cause of this vitamin reduction was also ascribed to the release of oxidases. G. N. Jenkins, of the Saint Bartholomew Medical College, has investigated the problem anew.[2] His first discovery was that there is just as much destruction of vitamin *C* when well-boiled vegetables are masticated; so obviously this cannot be put down to liberation of oxidases which are heat-sensitive. What might the causes be—drainage down the œsophagus, absorption by the mouth, the presence in the saliva of something which interferes with the quantitative analytical technique, or oxidation of the ascorbic acid by a substance present in the saliva or already in the food but not of enzyme character? Further investigation showed that it was the presence of nitrites in the saliva which was responsible. But nitrites will attack ascorbic acid only in strong acid solution, and then came enlightenment. It was the metaphosphoric acid used in the analytical procedure which activated the salivary nitrite and made this operative on the vitamin. So actually there is no, or very little, reduction of vitamin *C* through mastication. This story deals with a small detail in biochemical research, but it offers a salutary lesson on the value of unhurried experimentation.

SEDATION IN PSYCHOTHERAPY.

IT is probable that more sedatives are used today than any other type of drugs. Perhaps the commonest uses are in the relief of anxiety or tension and in the treatment of insomnia, though in both these instances the giving of temporary rest is by no means synonymous with the cure of the condition. Roy R. Grinker, in writing of sedation as a technique in psychotherapy, points out that sedative drugs first found their place in therapeutics as a substitute for the crude forms of physical restraint.[3] Today we are happily far from the days of chains for the mentally distraught, but though even the simplest and most gentle restraining devices are used with great hesitation, it cannot be said that "chemical restraint", as Grinker calls it, is always recognized for what it really is. This author emphasizes the value of the appropriate sedative as a means of uncovering the hidden sources of the patient's anxieties, in order that he may be helped to master them.

The pharmacology of the common sedatives has been taught and written of so frequently that the subject might be thought to be trite, but consideration of the light-hearted use of these powerful substances shows that full realization of its importance is perhaps not universal. The prolonged action of bromides, for example, with their replacement of chlorides in the blood, is most significant, for a change in water or chloride balance may precipitate bromide intoxication. Bromide poisoning is not an uncommon condition, as has been shown by a number of authors, including C. Sippe and J. Bostock in this journal some years ago.[1] Today the barbiturates are much more popular, and deservedly, but they have their risks. Histological studies have shown both in animals and man that the toxic influence of this drug group may cause definite and even severe damage in the nervous system. This is, of course, in the case of prolonged or excessive dosage. Tolerance is soon established for barbiturates and therefore some degree of habituation may occur. The risk of uncomfortable or undesirable side-effects is naturally greater when the drug is used to cover up symptoms. The advice that the medicine should be suspended for a brief interval, even if it is to be further continued, is not always given. Lastly, the dual action of the barbiturates on cortex and diencephalon is important, as this constitutes one of the great advantages in their use, and it is in connexion with this property that Grinker values them in psychiatric use. He refers briefly to the various methods that may be used in sedation. Continuous sedation is one of the commonest, even though it may do little in many cases other than to hide the patient's anxiety from himself, his friends and his physician. From the relief of sudden and overwhelming fear or anxiety the indication is much more sure and logical; the results in the handling of fear states under action conditions have shown this. But most of the worry states of daily life are not so readily reversible. Grinker doubts if cortical depressants may not be actually harmful, since the mechanisms for the control of anxiety have no opportunity to regain strength. In children, he points out, the capacity to learn is reduced by such drugs; so too it may be in adults who have to solve a problem of life.

Another common technique is that of sedation for insomnia. The temporary use of a sedative to favour sleep may further the proper relation between the doctor and the patient with his problems, but it is not the whole end of treatment. The advantage of combining a quickly acting drug and one whose action is prolonged is stressed, provided an adequate dose is given. Such a dose will usually be greater than the pharmacopœial minimum, which in acute cases may be quite ineffective and unsatisfactory to all parties. Continuous sleep is next mentioned by Grinker, but he condemns it as not effective in treatment. He considers that such a method tends to favour the immobilization reaction seen in lower animals, and also, with certain differences, sometimes in man. Therapeutic stupor in his hands has not been successful in uncovering the underlying reasons for the patient's symptoms. Last, he deals with the uncovering techniques, in particular the use of "Sodium Pentothal" or similar drugs. This is a technical procedure requiring adequate knowledge and experience, and also the correct temperament on the part of the therapist, who must know how to favour the abreaction of the patient. The handling of the abreaction is also most important, for a perfectly coherent explanation and understanding of the mechanism of the patient's anxiety are in vain unless it is accepted by his own ego. It is not suggested here that it is a simple matter of "every doctor his own psychiatrist". It is, however, important that we should all see clearly in this matter of sedation even for the bearers of the minor psychological burdens of this kind. Sedatives are powerful weapons; they should be carefully used, and if the occasion warrants the use of a more deft and experienced hand, the appropriate aid should be sought. Such drugs are not, as Grinker concludes, "a means of quieting the patient and thus making him less disturbing to his doctor".

[1] M. Pyke: "Food Supplies for Collective Feeding", *Proceedings of the Nutrition Society*, Volume I, 1944, page 92.

[2] G. N. Jenkins: "Effect of Mastication on the Ascorbic Acid Content of Raw Vegetables", *The Biochemical Journal*, Volume XL, 1946, page 415.

[3] *Bulletin of the New York Academy of Medicine*, April, 1946.

[1] THE MEDICAL JOURNAL OF AUSTRALIA, January 16, 1932.

Abstracts from Medical Literature.

MEDICINE.

Sulphonamide Therapy.

O. J. PENNA AND F. CHRISTOPHER (*The Journal of the American Medical Association*, April 20, 1946) discuss alkalinization of urine during sulphonamide therapy. Crystallization of sulphonamides in the urine may irreparably damage the kidneys. Sulphonamides as well as acute infections tend to acidify the urine. Crystallizations can be reduced to a minimum if the urine is kept neutral or alkaline and adequate daily urine excretion is kept up. Sulphadiazine produces less crystalluria than sulphathiazole. Sodium bicarbonate 12 to 22 grammes given daily by mouth, or two intravenous doses of 7·5 grammes of sodium bicarbonate in 100 millilitres of water in twenty-four hours, keep the urine alkaline and double the solubility of sulphadiazine. In a series of tests with the above doses of sodium bicarbonate, six grammes of sulphadiazine given orally every day for five days caused crystals to appear in the urine in 20% of patients when sodium bicarbonate 3·75% in 50 millilitres of water was administered intravenously twice a day, but no crystals appeared when 7·5 grammes were given twice a day. The fluid intake of the patients was about 2,500 millilitres per day (roughly four pints). Sodium bicarbonate was the most effective alkali tried.

Coronary Sclerosis.

W. DOCK (*The Journal of the American Medical Association*, July 13, 1946) has discussed the predilection of atherosclerosis for the coronary arteries. Coronary disease is far more frequent in men than in women. It has been shown that the intima of the coronary arteries is much thicker than that of other arteries and that this thickness increases with age. The coronary arteries of males have thicker intima than those of females, and in a series of post-mortem examinations of young soldiers it was found that small atheromatous patches in the coronary arteries were not infrequent even at the age of eighteen years. Hypertension and disordered cholesterol metabolism favour coronary atheroma, and these abnormalities have a familial tendency and may be induced by dietary habits, so that the thicker coronary artery in males, hypertension, disordered cholesterol metabolism and dietary habits require further study in coronary disease.

Diabetic Acidosis.

JOHN PETERS (*The American Journal of Digestive Diseases*, May, 1946) discusses the treatment of diabetic acidosis. When serious symptoms develop or threaten in diabetic acidosis, 25 grammes of glucose in 10% solution with 50 units of insulin should be given intravenously at once. Saline solution is also injected subcutaneously in large amounts; if it is not absorbed, it indicates an inadequate circulation, and transfusion is indicated. Saline solution is not given intravenously in order to avoid embarrassing an impaired circulation or reducing the serum protein content. After the first dose of insulin glucose is given at the rate of ten grammes per hour until the blood sugar level begins to fall, when more glucose is given. Joslin has said that in diabetic coma insulin is paramount in treatment. He gave about 200 units in the first three hours. The chief point is to give insulin early and to give enough of it, so that advanced coma never has a chance to develop.

The Neutrophile Leucocytes in Tuberculosis.

R. BENDA AND D. A. URQUIA (*La presse médicale*, June 8, 1946) claim that the presence of tuberculosis in the body may be diagnosed (even before a reaction to tuberculin has developed) and that its tendency to progress or to regress may be estimated in some measure from a study of the granules in the cytoplasm of the neutrophile leucocytes. They recognize three principal types of neutrophile leucocytes, considering them according to the number and size of their granules, namely, a "normal" type in which the granules are scattered like fine dust through clear cytoplasm, a "frankly pathological" type in which the granules are unequal, irregular and conglomerate and increased in number and volume, and an "intermediate" type in which the granules are more numerous than normal, though not enlarged nor conglomerate, and in which the cytoplasm is not quite clear and is of an old rose colour. The normal "granulogram" shows 70% to 100% of normal neutrophile cells and not more than 5% of the pathological type. When the intermediate type predominates tuberculosis is present and is recent, old, attenuated or "cured"; when the "pathological" type is present in excessive numbers, the disease is, according to the authors, present in a serious form.

Hæmatological and Clinical Characteristics of Leuchæmia.

RUSSELL L. HADEN (*American Journal of Roentgenology*, April, 1946) states that leuchæmia is a disease of the leucopoietic system characterized by the loss of normal physiological control of leucocyte formation. Normally there is active orderly growth of white cells in the marrow, spleen, lymph glands and reticulo-endothelial system. Only mature cells reach the blood stream. In an acute need for defence against infection and toxæmia the leucopoietic tissues can supply enormous numbers of mature cells. The hyperplasia, however, is still under normal physiological control. Normally five to ten billion polymorphonuclear cells and an equal number of lymphocytes are supplied daily. If needed, many times this number can be supplied. In leuchæmia there is a disorderly overgrowth of leucopoietic tissues suggesting a neoplastic process. This is due either to some unknown stimulation or to a loss of normal physiological control. Leuchæmia is a generalized disease and may affect any part of the body. It is characterized primarily by toxæmia and cellular infiltration of organs and other body tissues. The bone marrow is always involved. It is usually hyperplastic, but may be aplastic though immature. The typical blood finding is leucocytosis with immature cells such as myeloblasts, myelocytes, lymphoblasts, monoblasts, and intermediate cells in the circulation. Leucocytosis is, however, often absent, especially in the acute types. In the 400 patients in the author's series the leucocyte count was below 10,000 per cubic millimetre in one-third. In 100 patients with acute lymphoid or acute myeloid leuchæmia the count was below 10,000 in over one-half the cases. Anæmia is almost always present, and thrombopenia is common. The signs and symptoms of leuchæmia are principally the result of anæmia, hæmorrhage, and infection due to toxæmia and cellular infiltration. The greatest variety of clinical pictures is encountered, so that little is characteristic of a patient with leuchæmia. Acute lymphoid leuchæmia is a disease of childhood. Anæmia, bleeding and arthritis are common symptoms. Acute myeloid leuchæmia occurs in all ages and presents the greatest variety of symptoms and clinical findings. Chronic lymphoid leuchæmia is often a very mild disease and runs a moderate though fatal course. Enlargement of glands and spleen is the outstanding feature. Chronic myeloid leuchæmia is characterized by a marked toxæmia causing almost constant fever and anæmia. Oral infections with hypertrophy of the gums are prominent symptoms in monocytic leuchæmia. The spleen is seldom palpable. The leucocyte count is usually not very high. The anæmia is often macrocytic.

The Bactericidal Action of Vitamin D.

W. RAAB (*Diseases of the Chest*, September-October, 1946) describes experiments which show that vitamin *D* (activated ergosterol) is bactericidal *in vitro* and *in vivo* to *Mycobacterium tuberculosis, Proteus vulgaris, Bacillus aerogenes, Staphylococcus* and non-hæmolytic streptococci. Intrapleural injection of the vitamin in several persons suffering from tuberculous empyema caused the pus to become sterile.

H. J. WALLACE (*The Lancet*, July 20, 1946) reports successful results from the administration of large doses of calciferol (50,000 units twice daily for some months) to patients suffering from tuberculous glands and sinuses.

Postural Hypotension.

T. EAST AND W. BRIGDEN (*The British Heart Journal*, April, 1946) report a case of the syndrome called postural (or orthostatic) hypotension, which consists of the triad of anhydrosis, impotence and a profound fall in blood pressure on standing up. The patient was a man, aged fifty-seven years. For four years he had never sweated, and for many years previously he had sweated only on the left side of his body, his fellow workers having observed that only one side of his shirt became damp. He had had no sexual activity or desire since the age of thirty-seven. At the age of fifty he began to suffer from attacks of giddiness, weakness and tremulousness, which came on only when he was standing, and sometimes he lost consciousness. The authors point out that in this syndrome the distribution of blood in the arterial system is such as to suggest that the arteries are without vasoconstrictor control, and, indeed, the normal control is defective. The site of the lesion is uncertain and

may vary, but is in the central nervous system. It was found that amphetamine ("Benzedrine") and ephedrine provided relief of symptoms. The scheme of dosage found most satisfactory consisted of five milligrammes of "Benzedrine" at 8, 9 and 11 a.m. and thirty milligrammes (a quarter of a grain) of ephedrine at 1, 3 and 5 p.m.

Survival of Penicillin-Sensitive Organisms in Dried Penicillin.

H. PROOM (*The Lancet*, July 6, 1946) has shown that dried pathogenic penicillin-sensitive organisms may remain viable for a considerable period—at least ten weeks—in contact with commercial dried penicillin. This mixture when dissolved and injected into animals may cause infection. In practice the risk of infection from contaminated dried penicillin is small; but it is sufficient to make it advisable to test the sterility of dried penicillin before use.

The Control of Epidemic Poliomyelitis.

J. DEENY AND J. D. MCCORMACK (*The Lancet*, July 6, 1946) have devised a scheme for controlling outbreaks of poliomyelitis. First, patients are at once isolated in hospital and their homes thoroughly disinfected; second, family contacts are placed in quarantine for a week and in partial quarantine for two weeks thereafter; third, information is given to doctors and to the public in the area of the outbreaks so that all patients with pyrexial illness may be seen at once; fourth, children from the area are excluded from schools and other public places; fifth, the public are advised over the radio, through the newspapers and by leaflets to take care in the handling of food, especially to protect it from contamination by flies, to boil all milk, and to wash the hands carefully in running water, especially after visiting the lavatory (this advice is directed particularly to those who handle and prepare food); sixth, in districts in which a piped water supply is not available the public are advised to boil all water used for domestic purposes; seventh, it is advised that fæces be treated with disinfectants and that in rural districts fæces be covered with fresh earth to prevent access by flies; eighth, flies in the area are destroyed with DDT; ninth, all cases are notified to the central health authority. The authors were able to test their scheme during a small outbreak of the disease in county Dublin, with an extension to county Clare. The results, they believe, were encouraging, but did not establish the efficacy of the procedure.

The Penicillin Treatment of Empyema.

BRUCE BROWN, EDWIN M. ORY, MANSON MEADS AND MAXWELL FINLAND (*Annals of Internal Medicine*, March, 1946) discuss the penicillin treatment of empyema and present a report of twenty-four cases in which this treatment was adopted. The results of treatment are correlated with similar cases collected from an analysis of the literature. The authors administered the penicillin intrapleurally, intramuscularly or by both of these routes. It was found that between 50% and 60% of empyemata due to the pneumococcus, hæmolytic streptococcus and staphylococcus were cured without operative drainage. However, non-operative cures were less frequent and more of the patients died, in the presence of putrid empyema and of mixed infections. The general condition of patients with empyema improved markedly after treatment with penicillin and aspirations were started, and even those with putrid empyema were probably much better operative risks as a result of preparation with this form of therapy. In favourable cases, sterilization of the empyema fluid was usually accomplished and the volume which could be aspirated diminished appreciably after three intrapleural instillations or less. The changes in the fluid following therapy were not uniform and could not always be relied upon as a guide for further therapy or as an indication for operation. The foul odour of the putrid empyema cleared promptly after penicillin therapy was started. In such cases of empyema that were cured by aspirations and penicillin alone, the hospital course and convalescence were considerably shorter than in those in which operative drainage was used. It was found that significant levels of penicillin were maintained in the blood for several hours after intrapleural injection in amounts of 50,000 units or more, but the concentration in the blood and its duration depended on the size of the dose and probably on the size and character of the empyema cavity. The authors conclude that systemic therapy is probably not essential in most cases, particularly if intrapleural injections of 100,000 units or more are given at twenty-four or forty-eight hour intervals.

Quinidine in Congestive Failure with Auricular Fibrillation.

JOHN MARTIN ASKEY (*Annals of Internal Medicine*, March, 1946) discusses the use of quinidine in the treatment of auricular fibrillation in association with congestive heart failure. His study concerns itself with a statistical evaluation of the dangers of quinidine, particularly in the presence of congestive failure and serious heart disease, and he attempts to establish positive criteria for treatment. It is thought that embolism is a greater hazard if auricular fibrillation is allowed to continue than if the heart rhythm is restored to normal. The risk of embolism is a constant one as long as the arrhythmia continues, whereas the risk of embolism from quinidine is confined to a period of a few days following return to normal rhythm. A review of the statistics suggests that the risk of eventual embolism is about 4% if quinidine is given for auricular fibrillation and approximately 15% to 20% if the auricular fibrillation is allowed to persist. The author believes that, in view of the absence of convincing data to the contrary, the danger of embolism cannot be cited as a contraindication to the use of quinidine. The fear of sudden death is the main contraindication to the use of quinidine for auricular fibrillation if congestive failure is associated with it, but if the natural risk of sudden death from the condition itself is greater than the risk from the drug, then quinidine is indicated. The author refers to fifteen desperately ill patients, in whom repeated embolism, long-standing auricular fibrillation, marked congestive failure, and conduction defects were not considered contraindications because the danger of death from the condition in each instance was considered greater than the danger of death from the drug. The decision to use quinidine was based upon individual considerations and not upon general contraindications. The author states that quinidine is a drug feared much more than it deserves to be, and that probably it is not used in many instances where it should be. Toxic effects such as nausea, tinnitus and diarrhœa, if mild, can be ignored, but if they persist they will disappear with withdrawal of the drug. Quinidine is apparently no more dangerous in the treatment of patients without congestive failure than the natural dangers of the heart condition itself. Therefore, there should be no objections to a trial of quinidine in the treatment of patients without congestive failure unless conduction defects are present, and if these defects are present it should not be given. The only real danger of the drug is that of sudden death, which is an important factor only in the presence of congestive failure or of conduction defects. Even in the presence of congestive failure, the liability of sudden death after quinidine is statistically little more than the natural risk of sudden death from the heart disease itself. Among patients with congestive failure who improve adequately with digitalis and rest, quinidine would seem unnecessary. If conduction defects are not present there would seem to be no reason why every patient with uncontrolled congestive failure should not be given a test with quinidine. It is suggested that the more desperately ill the patient, the more justifiable becomes the use of quinidine. Although a return to sinus rhythm cannot be expected to change the downward course of progressive heart disease, it can in certain instances relieve congestive failure not responding to other measures and can prolong life.

Clinical and Radiographic Diagnosis of Pericardial Effusion.

NATHAN M. FENICHEL AND BERNARD S. EPSTEIN (*Annals of Internal Medicine*, March, 1946) report on the clinical and radiological diagnosis of pericardial effusion and base their comments upon a review of the findings in a series of thirteen cases. All the patients had large pericardial effusions, and the most reliable sign found was the broad area of absolute dulness extending from the right mid-clavicular line to the left mid-axillary line. In this connexion the authors state that a flat percussion note should be sought to the right of the sternal border in suspected cases of pericardial effusion. Increased venous pressure revealed by distended neck veins and hepatic enlargement was a constant finding in the cases, and although all the patients were dyspnœic, only seven of the thirteen were orthopnœic. Ewart's sign may be elicited if the pericardial effusion is of inflammatory origin, and a paradoxical pulse is frequently present. The authors are of opinion that the radiological signs, which are usually described as indicative of pericardial effusion, may be difficult to evaluate, especially in the presence of a concomitant pleural or pulmonary pathological process. The artificial induction of hydropneumopericardium by the xiphoid approach is suggested as an additional radiological diagnostic measure.

XUM

Bibliography of Scientific and Industrial Reports.[1]

THE RESULTS OF WAR-TIME RESEARCH.

During the war a great deal of research was carried out under the auspices of the Allied Governments. It has been decided to release for general use a large proportion of the results of this research, together with information taken with former enemy countries as a form of reparations. With this end in view, the United States Department of Commerce, through its Publication Board, is making a weekly issue of abstracts of reports in the form of a "Bibliography of Scientific and Industrial Reports". This bibliography is now being received in Australia, and relevant extracts are reproduced hereunder.

Copies of the original reports may be obtained in two ways: (a) Microfilm or photostat copies may be purchased from the United States through the Council for Scientific and Industrial Research Information Service. Those desiring to avail themselves of this service should send the Australian equivalent of the net quoted United States price to the Council for Scientific and Industrial Research Information Service, 425, St. Kilda Road, Melbourne, S.C.2, and quote the PB number, author's name, and the subject of the abstract. All other charges will be borne by the Council for Scientific and Industrial Research. (b) The following reports may be obtained in approved cases without cost on making application to the Secondary Industries Division of the Ministry of Post-War Reconstruction, Wentworth House, 203, Collins Street, Melbourne, C.1. Copies of these are available for reference in public libraries.

Further information on subjects covered in the reports and kindred subjects may be obtained by approaching the Council for Scientific and Industrial Research Information Service, the Secondary Industries Division of the Ministry of Post-War Reconstruction, or the Munitions Supply Laboratories (Technical Information Section), Maribyrnong, Victoria.

PB 18324. ADAMS, J. K., *et alii.* A test-retest reliability study of the Bausch and Lomb ortho-rater with naval personnel. (Applied Psychology Panel: Selection and training of range-finder and radar operators. Report 6.) (N.D.R.C. Applied Psychology Panel Report 270. OSRD Report 3969.) August, 1944. 36 pp. Price: Microfilm, 50c.; Photostat, $3.00.

This memorandum is a report on the reliability of test-retest results of the occupational vision tests with the ortho-rater. The Bausch and Lomb ortho-rater tests include measures of far and near visual acuity, for both eyes and for each eye separately; measures of vertical and lateral phoria, far and near; a static depth test (stereopsis) and a test of colour vision. The tests and retests from which the data in the study were derived, were administered to candidates for training as fire controlmen at the Naval Training Centre, Sampson, New York. Owing to the homogeneity of the sampling, the usual correlation study of reliability is difficult to interpret, and, therefore, other statistical techniques were used. Analyses of the test-retest results indicate that: (i) the ortho-rater tests are sufficiently reliable as testing devices in the selection of candidates for training as fire controlmen-rangefinder operators; (ii) although significant differences between the means of several visual acuity tests do occur, the average differences are small and the standard errors of estimate for these tests are small enough to assure an acceptable high degree of accuracy in predicting scores on retests from scores on the original tests; (iii) the far and near point tests are of equivalent reliability; (iv) the signs of the coefficients of correlation are reduced by the homogeneity of the sample.

PB 18796. KAISER, HERMAN F. Report on radon leakage from Navy capsules. (Naval Research Laboratory Report M-2036.) January, 1943. 22 pp. Price: Microfilm, 50c.; Photostat, $2.00.

This report is concerned with a series of field and laboratory tests which were carried out to determine the extent of radon leakage in radium capsules owned and used by the Navy for γ radiographic inspection. The majority of the capsules tested showed leakage to a greater or less extent. Tests were carried out to determine the best means of sealing leaking capsules in steel cartridges. These showed that this may best be done by solder sealing the steel cartridges. The internal cavity of the cartridge must be kept to a minimum to avoid loss of radiographic definition.

PB 18832. COWGILL, GEORGE R. Effect of substitution of lead silver for tin lead solder on canned foods. Progress Report, February 19, 1943. (War Metallurgy Committee Research Report W-15.) March, 1943. 7 pp. Price: Microfilm, 50c.; Photostat, $1.00.

This progress report of work done by Yale University under contract with the War Production Board indicates that rats fed an artificial diet containing quantities of lead and silver are being ashed and then analysed. A method of feeding pellets in lumps of butter was found easier than the use of the stomach tube.

PB 18833. COWGILL, GEORGE, AND SALOMON, KURT. Effect of substitution of lead silver for tin lead solder on canned foods products: Final report. (War Metallurgy Committee Research Report W-53.) August, 1943. 57 pp. Price: Microfilm, $1.00; Photostat, $4.00.

Twenty-four groups of rats were used in a study of the possible toxicity of three lead alloys administered in the form of solder pellets containing respectively: (*a*) lead 93%, tin 5% and silver 2%; (*b*) lead 95%, tin 2·5% and silver 2·5%; and (*c*) lead 97·43% and silver 2·57%. The experiments are further described in this report. The rats receiving 300 parts of lead per million of diet in the form of solder pellets, proved to be quite similar to the control group fed on identical diet, but no lead, with respect to growth, concentration of blood hæmoglobin and the appearance of stippled cells, as well as with respect to the amount of lead stored in their carcasses. It was concluded that ingested solder of the compositions here studied as a source of lead is non-toxic for the young rat. All of the rats in another group which received lead acetate were definitely poisoned. Thirty-five pages of tables are included.

PB 19786. DAVIS, HALLOWELL, *et alii.* Physiological effect of exposure to certain sounds: Final report. (OSRD Report 889.) July, 1942. 82 pp. Price: Microfilm, $1.00; Photostat, $6.00.

Particular attention was directed to frequencies in the neighbourhood of 1,000 cycles, to intensities capable of sustained generation, and to durations of several seconds to a few minutes. In addition to possible lethal effects, the investigation sought for the production of deafness, either permanent or temporary, for temporary or permanent effects on the labyrinthine apparatus affecting posture and equilibrium, and any harmful or disturbing effects on the nervous system that might interfere with the performance of military duties. Guinea-pigs, rats and cats were used as experimental animals, and the physiological and anatomical findings have been correlated. A new method for physiological study of auditory fatigue and recovery was developed, but not exploited in the study of the effects of intense sound. The production of audiogenic (epileptiform) seizures in rats was studied and the intensities of sound at various frequencies within the audible range necessary to produce such seizures were determined. Human ears were exposed to loud sounds for various priods of time, and in addition to the observation of pain and other discomfort the resulting temporary deafness was measured by means of the audiometer. The parameters of frequency, intensity and duration of exposure tone in relation to the production of temporary hearing loss were studied in some detail. Preliminary observations were made on the effects of interruption of sound, and on the effectiveness of band spectra and of a continuous spectrum as compared with simple pure tones. Eight photomicrographs of lesions of the inner ear of guinea-pigs are attached to the report. The text is illustrated with graphs and tables.

PB 18366. LINDSLEY, DONALD B., *et alii.* Radar operator "fatigue": The effect of length and repetition of operating periods on efficiency of performance. (OSRD Report 3334; N.D.R.C. Applied Psychology Panel 121, Research Report 6.) January, 1944. 38 pp. Price: Microfilm, 50c.; Photostat, $3.00.

The purpose of this study was to determine whether long and repeated periods of operation of an a-scan oscilloscope result in loss of efficiency in performance or so-called "fatigue effects". It was desired to know when impairment of performance begins and what relationship it bears to the length and frequency of repetition of operating periods. The study indicated that: (1) Daily repetition of a four-hour period of a-scan oscilloscope operation caused a progressive loss of efficiency in the detection of signals and in the accuracy of determining the azimuth or bearing of targets represented by the signals. (2) Loss of efficiency was related to the length and repetition of the operating periods and revealed itself by an increase in the number of signal omissions, an increase in the rate of making omissions, a decrease in accuracy of azimuth or bearing determinations, and by a general increase in variability of performance. (3) Impairment of performance first became significant with repeated operating periods of forty minutes in duration

[1] Supplied by the Information Service of the Council for Scientific and Industrial Research.

for a group operating in the afternoon. (4) Loss of efficiency did not become apparent until the third day of repeated four-hour operating periods. Drawings, graphs and tables illustrate the report.

PB 18358. LINDSLEY, DONALD B., *et alii.* Visual status of ASV radar operators. (Applied Psychology Panel: Selection and training of oscilloscope operators. Research Report 9.) (N.D.R.C. Applied Psychology Panel Report 136. OSRD Report 3443B.) March, 1944. 11 pp. Price: Microfilm, 50c.; Photostat, $1.00.

As a result of tests it was found that a group of 66 ASV oscilloscope operators showed no significant differences in visual acuity or muscle balance when compared to a group of 112 non-operators. Nineteen men, the most highly experienced operators in the group with 500 or more hours in the air, failed to show deleterious effects of long-continued operations. These results bear out the conclusion of a previous study on air-warning operators to the effect that oscilloscope operation does not produce persistent effects on vision.

PB 11341. MARQUAND, C. B., *et alii.* Solid oxidizing agents, their stability and their theoretical and practical value against liquid Lewisite burns. December 5, 1942. (CWS MD (EA) Memorandum Report 72.) 1942. 41 pp. Price: Microfilm, 50c.; Photostat, $3.00.

Solid peroxides and solid oxidizing agents were tested in the oven at 50° C. for stability and on the skin of rabbits and on human skin to determine their prophylactic action against applications of liquid Lewisite. Sodium pyrophosphate peroxide and a mixture of sodium perborate and sodium dihydrogen phosphate showed some efficacy in these respects. Certain theoretical and practical applications were found which act as useful criteria for further work. Tables are used throughout the report. A bibliography is attached.

PB 18800. TOUSEY, R. Effect of cathode ray tube screens on night vision. (Naval Research Laboratory Report H-2226.) January, 1944. 21 pp. Price: Microfilm, 50c.; Photostat, $2.00.

The effect on night vision of CRT screens of various colours and brightness of trace was investigated in the laboratory. Actual radar screens of several types were observed in the field under night-time conditions. In general it was found that green trace CRT screens can be made satisfactory as regards night vision by the use of an orange filter and P-7 screens by means of a red filter. Application to actual radar installations is discussed. The work is divided into three parts: first, laboratory experiments on a variety of CRT screens; secondly, observations on the effect on night vision of several actual radar screens and the use of filters; thirdly, information gathered from various sources concerning those radar installations, for which the question of preserving dark adaptation may be important. References, tables and graphs are included.

PB 15166. U.S. War Department. Geographical distribution of certain diseases (outline maps only). June, 1944. 15 pp. Price: Microfilm, 50c.; Photostat, $1.00.

This pamphlet consists of outline maps, prepared by the Medical Intelligence Branch, Preventive Medicine Division, Office of the Surgeon General, U.S. Army, showing geographical distribution of the following diseases: cholera, dengue, filariasis, leishmaniasis, malaria, mite typhus, plague, relapsing fever, schistosomiasis. trypanosomiasis, typhus fever, yaws and bejel, and yellow fever.

PB 15165. U.S. WAR DEPARTMENT. Health precautions for African and Asiatic countries along southern and eastern Mediterranean Sea, Red Sea and Persian Gulf. (Pamphlet 8-3.) April, 1943. 21 pp. Price: Microfilm, 50c.; Photostat, $2.00.

Precautionary measures to be taken by military personnel and travellers in these areas against venereal diseases, diseases carried by insects, animals, water, food and bathing are presented. For similar information for other areas, see PB 15163-4.

PB 15163. U.S. WAR DEPARTMENT. Health precautions for Central and South Africa and the west coast of Africa. (Pamphlet 8-1.) April, 1943. 20 pp. Price: Microfilm, 50c.; Photostat, $2.00.

Military personnel and other travellers in Central and South Africa and on the west coast of Africa are exposed to serious health hazards. This pamphlet is designed to cover the potential hazards of a large general area. The subjects discussed are: water, water economy under desert conditions, foods, clothing, bathing, swimming, housing, insect carriers of disease, diseases acquired from animals, venereal diseases, sunburn, sunstroke, heat exhaustion, minor wounds, vaccinations, and summary of immunizations. For similar information for other areas see PB 15164-5.

PB 15164. U.S. WAR DEPARTMENT. Health precautions for Central and South America and Caribbean Sea Area. (Pamphlet 8-2.) April, 1943. 18 pp. Price: Microfilm, 50c.; Photostat, $2.00.

This pamphlet indicates the potential hazards of the water supply, foods, clothing, bathing and swimming, housing, insects, other vectors of disease, venereal diseases, sunburn, sunstroke, heat exhaustion, and minor wounds. Precautionary measures are outlined, and a summary of immunizations is included. For similar information for other areas, see PB 15165 and PB 15163.

PB 16794. BENZINGER, TH. Medical division of the experimental station of air force Rechlin. No date. 19 pp. Price: Microfilm, 50c.; Photostat, $2.00.

This report regards the Rechlin establishment, started March, 1934, and is translated from German in the following parts: I. Organization, II. working conditions, III. tasks and results of the applied research, and IV. scientific tasks and results. None of the enclosures mentioned in the body of the report are attached. It covers the work done in simulated altitude flight, giving results of the investigations and recommendations.

PB 19408. KOLLER, G. *Hypophysentätigkeit und Erblindung (Reichsforschungsrat)* (The activity of the hypophysis and blindness). (ALSOS Mission, RFR 507 22.) December, 1944. 5 pp. Price: Microfilm, 50c.; Photostat, $1.00.

The report defines three different hormones developed by the hypophysis and describes tests made with rats and frogs. The tests proved as a major result that the water-regulating hormone becomes increasingly ineffective if the tested animals are kept in absolute darkness over a period of time. This fact resulted in the author's theory that if disturbances in the water system occur after going blind the origin of such blindness is to be found in the hypophysis. In German.

PB 18563. U.S. WAR DEPARTMENT SPECIAL OPERATIONS. Civil affairs guide: Denazification of the health services and medical profession of Germany. (Pamphlet 31-158.) June, 1945. 75 pages. Price: Microfilm, $1.00; Photostat, $5.00.

This report briefly outlines the racial theories and racial laws which provided the basis for the changes and innovations the Nazis introduced into the health system of Germany and recommends the measures which will eliminate these salient Nazi features from the system. In addition recommendations are made to cope with the health situation and to prevent the spread of epidemics among United Nations armed forces. This pamphlet was prepared by the Enemy Branch, Foreign Economic Administration.

PB 18633. U.S. ARMY TECHNICAL INTELLIGENCE CENTRE, TOKYO. Japanese medical equipment: Case, plastic, malarial prophylactic. (Report 168.) January, 1946. 3 pp. Price: Microfilm, 50c.; Photostat, $1.00.

This item indicates that the Japanese used both quinine and "Plasmoquine" combined as malarial suppressive therapy. The amount of the drug carried was supposed to be sufficient for thirty days' suppressive therapy with quinine and sixty days' suppressive therapy with "Plasmoquine". A photograph of the kit is attached to the report.

PB 12371. WESCOE, W. C., *et alii.* Studies on di-iso-propyl fluorophosphate and other cholinergic agents. (CWS Contract W-49-057-CWS 39. Bimonthly progress report 1.) January, 1946. 3 pp. Price: Microfilm, 50c.; Photostat, $1.00.

This is a brief report of studies made on cholinergic agents, including DFP, di-iso-propyl fluorophosphate. The structural formula for prostigmine reveals an analogy to the choline esters. Experiments have been carried out to investigate a possible common reaction to all such type compounds. Cholinesterase inhibition was also produced by therapeutic amounts of a synthetic choline ester, carbamylcholine in man. These observations have important clinical implications for the optimal use of "Prostigmin" in *myasthenia gravis.*

PB 15171. U.S. WAR DEPARTMENT. Reconditioning training programme for class 1 and 2 patients, A.S.F. regional and station hospitals (4 weeks). (Army Service Forces Manual M8.) June, 1945. 10 pp. Price: Microfilm, 50c.; Photostat, $1.00.

The purpose of this programme was to furnish a general guide for the graduated training of patients in an advanced stage of convalescence from serious illnesses, injuries or surgical procedures so that they may be returned to a duty status in the shortest possible time and in the best possible physical and mental condition. Programme of instruction covering educational and physical reconditioning is outlined.

PB 19063. U.S. WAR DEPARTMENT. MEDICAL CORPS. Dental X-ray machine. (Tech. Manual 8-634.) January, 1945. 47 pp. Price: Mimeo, 15c.

This manual contains information on the operation and maintenance of the equipment, as well as descriptions of the major units and their function in relation to the other components of the equipment. They apply to dental X-ray machines manufactured by H. G. Fischer and Company, X-Ray Manufacturing Corporation of America and Weber Dental Manufacturing Company. Appendix I contains information on shipment and storage, disassembling, and packing and crating the various models. The manual is illustrated throughout by photographs and drawings and keyed with nomenclature to aid in understanding the text.

British Medical Association News.

SCIENTIFIC.

A MEETING of the New South Wales Branch of the British Medical Association was held on May 23, 1946, at the Royal Prince Alfred Hospital. The meeting took the form of a series of clinical demonstrations by members of the honorary medical staff of the hospital. Parts of this report appeared in the issues of November 16 and November 30, 1946.

Chronic Suppurative Labyrinthitis; Labyrinthectomy.

DR. GARNET HALLORAN first showed a male patient, aged fifty-four years, who for eight years had suffered from severe headache, from attacks of vertigo and from total deafness in the right ear. When he was examined on September 24, 1945, pus was present in the middle ear on the right side. The right ear was totally deaf, and spontaneous nystagmus towards his left side was observed. Bárány tests revealed only a slight reaction from the right static labyrinth. Headache was severe, and was mostly referred to the parietes and the occiput on the right side. Attacks of vertigo completely incapacitated the patient. On October 2 a right radical mastoidectomy was performed. The middle ear cleft was found to be filled with granulations, no drum remnants were seen, and necrotic malleus and incus were removed.

On January 7, 1946, the patient was readmitted to hospital suffering from severe vertigo, right-sided headache and drowsiness. His condition aroused suspicion of an intracranial complication. His cerebro-spinal fluid was turbid, and the pressure was 110 millimetres of water; it contained no white blood cells. Total deafness of the right ear and nystagmus to his left side existed as previously. Sulphadiazine therapy was instituted. It was decided that total destruction of the labyrinth was necessary, as severe vertigo and great headache persisted. On March 5 labyrinthectomy was performed according to Neumann's technique, the sulphadiazine treatment being maintained. The patient rapidly lost his nausea and had no more attacks of incapacitating vertigo. In three weeks he could walk slowly and felt well. Two months later the right-sided chronic headache had not recurred. Attacks of vertigo had ceased, he had gained nine pounds in weight, and progressive improvement in walking was evident as the function of compensatory senses improved.

Intrinsic Carcinoma of the Vocal Cord.

Dr. Halloran then showed a male patient, aged forty-six years, who complained of progressive hoarseness of his voice over a period of nine months. Examination of the larynx revealed a neoplasm restricted to the anterior two-thirds of the right vocal cord. Movement of the cord was not impaired. There was no subglottic extension, and the growth did not extend beyond the anterior fornix. Biopsy revealed a mass of squamous cells which varied considerably in size and shape. Mitoses were present, prickle cells were numerous and there was some attempt to form keratin in the centre of the epithelial masses.

A diagnosis of squamous-cell carcinoma (fairly mature) was made (Broder's classification, Grade III). The growth was considered suitable for treatment either by protracted fractional irradiation or by excision by laryngo-fissure. The former method was decided upon, and deep X-ray therapy by the protracted dosage technique was commenced on March 18, 1946. The factors used were 375 kilovolts, five milliamperes, a filter of three millimetres of copper and one millimetre of aluminium, and a focal skin distance of fifty centimetres. Irradiation was given to three fields, each a five-centimetre circle. Two lateral fields were used, one left, one right, aimed directly at the posterior ends of the vocal cords, and an anterior field was used directly over the thyreoid cartilage. The skin dose on each lateral field was 3,500*r*, and that on the anterior field was 1,600*r*. Treatment was commenced with a daily dose of 250*r* to one field, gradually increased to 400*r* on one field. The estimated tumour dose of 6,100*r* was given over eight weeks; a dose of 5,000*r* was given in one month, and a further 1,100*r* were given three weeks later. The patient's general condition throughout was excellent, and no systemic reactions occurred. On May 23 examination of the cord revealed evidence of post-irradiation reaction. The outline of the original lesion was overshadowed by the generalized redness of the reaction throughout the whole cord; slight retardation of movement and slight subglottic congestion were present.

Fracture of the Superior Part of the Maxilla; Comminution of the Infraorbital Plate; Prolapse of Orbital Fat into the Antrum.

Dr. Halloran finally showed a male patient, aged thirty-two years, who had been knocked down by a motor-car on May 30, 1946. He did not lose consciousness. X-ray examination revealed multiple fractures of the left malar bone, the left infraorbital plate and the nasal bones, with considerable malalignment of malar and infraorbital margins.

Operation was performed on the same day for elevation of the depressed malar bone and removal of loose bony fragments from the antral cavity. Prolapsed orbital fat was raised by antral packing maintained for two weeks. Access to the orbital floor was made via the antral cavity through a Caldwell-Luc incision. The orbital floor was found extensively comminuted, a large gap being present through which orbital fat had prolapsed into the antral cavity. To prevent enophthalmos and to promote fibrosis as a support for the prolapsed tissues, the fat was packed upwards for two weeks with gauze impregnated with *Tinctura Benzoini Composita*. Sulphanilamide powder was also insufflated. The malar and nasal bones having been elevated, fixation of the superior part of the maxilla was desirable. At the United Dental Hospital, an open metal ferrule splint with soldered metal extensions to a skull cap was applied. At the time of the meeting all gauze had been removed and the antral incision had healed. Alignment was good.

NOTICE.

THE General Secretary of the Federal Council of the British Medical Association in Australia has announced that the following medical practitioner has been released from full-time duty with His Majesty's Forces and has resumed civil practice as from the date mentioned:

Dr. E. Murray-Will, 175, Macquarie Street, Sydney (October 14, 1946).

Naval, Military and Air Force.

APPOINTMENTS.

Surgeon Captain Denis Adrian Pritchard has been appointed honorary physician to His Majesty the King.

Acting Surgeon Captain Lionel Lockwood has been appointed honorary surgeon to His Majesty the King.

Post-Graduate Work.

POST-GRADUATE COMMITTEE IN MEDICINE OF THE UNIVERSITY OF ADELAIDE.

THE Post-Graduate Committee in Medicine of the University of Adelaide announces that courses suitable for candidates for higher degrees will be held in 1947 as follows.

Course in Advanced Medicine.—A course will last for a period of twelve weeks, beginning on Monday, January 20, 1947, at the Royal Adelaide Hospital. This will end early in April and just after the commencement of the examination for the M.R.A.C.P. which will be held in Adelaide. The course will consist of the following items:

1. Case-taking. Two sessions per week under the direction of Dr. F. R. Hone, Dr. G. A. Lendon, and Dr. K. S. Hetzel and Dr. F. H. Beare.
2. Post-graduate ward round. One per week with Dr. F. R. Hone, Dr. G. A. Lendon, Dr. A. R. Southwood and Dr. K. S. Hetzel.
3. Applied morbid anatomy. One weekly session by Sir Trent de Crespigny.
4. Neurology. Four lecture-demonstrations by Dr. E. Britten Jones.
5. Tutorials. Two tutorials per week by Dr. C. B. Sangster, Dr. M. E. Chinner, Dr. R. A. Pellew and Dr. J. M. Bonnin.
6. Electrocardiography. Five sessions by Dr. E. F. Gartrell.
7. Ocular fundi. Three lecture-demonstrations by Dr. A. L. Tostevin.

8. Infectious diseases. Three sessions by Dr. A. H. Finger.
9. X-rays. Four demonstrations by Dr. J. S. Verco.

In addition to the above, certain parts of the continuous refresher course will be included. The parts that will be useful to candidates for higher degrees are: (i) lecture in medicine, one per week; (ii) post-mortem material, a weekly demonstration by Professor J. B. Cleland, Dr. J. B. Thiersch and Dr. J. M. Dwyer; (iii) diseases of children, a weekly lecture; (iv) clinical pathology, four sessions by Dr. J. B. Thiersch; (v) bacteriology, five lectures by Miss Nancy Atkinson; (vi) psychiatry, five lecture-demonstrations by Dr. F. H. Beare and one by Dr. H. M. Birch.

Physiology. Certain of the lectures in physiology given for the Part I M.S. course will be suitable for candidates for a higher degree in medicine, and they are invited to attend.

A detailed programme of subject matter, lecturers, times and dates can be obtained from the Medical Secretary.

Course in Anatomy and Physiology Suitable for Part I M.S.—The Post-Graduate Committee in Medicine will give a course commencing on February 3 for a period of three months.

1. Physiology. A series of 44 lectures will be given by Professor Sir Stanton Hicks, Dr. W. A. Dibden and Dr. M. Draper, and will be held in the Physiology Department, University of Adelaide, from 9 to 10 a.m. on three mornings a week.

2. Anatomy. Sixty-one lectures will be given by Professor Abbie and Dr. J. R. Barbour. These lectures will be held at the Anatomy School at 4.30 p.m. five days a week.

Applications should be forwarded to the Medical Secretary, Post-Graduate Committee in Medicine, Institute of Medical and Veterinary Science, before January 1, 1947.

The fee for the course in advanced medicine is £31 10s., and that for the course in anatomy and physiology is £25.

Cheques should reach the Registrar, the University of Adelaide, prior to the day of commencement of the course to be undertaken.

POST-GRADUATE COMMITTEE IN MEDICINE IN THE UNIVERSITY OF SYDNEY.

COURSE FOR GENERAL PRACTITIONERS.

THE Post-Graduate Committee in Medicine in the University of Sydney announces that a course for general practitioners will be held at Sydney from January 13 to April 4, 1947, inclusive. The course will include medical practice in its general, economic and business aspects; medical conditions; points in radiology and X-ray therapy; dermatology; anæsthesia; oto-rhino-laryngology; ophthalmology; psychiatry; surgical conditions; physical therapy; orthopædic surgery; urology; neurology; gynæcology; obstetrics; pædiatrics. Lectures will be given each week-day, sometimes all day.

Particulars of the course may be obtained from the Honorary Secretary, Post-Graduate Committee in Medicine in the University of Sydney, 131, Macquarie Street, Sydney. Telephones: B 4606, BW 7483.

Special Correspondence.

CANADA LETTER.

FROM OUR SPECIAL CORRESPONDENT.

THE outstanding medical event in Canada this month was the convocation address at the University of British Columbia by Professor Wilder Penfield, Director of the Montreal Neurological Institute. After receiving the honorary degree of Doctor of Science, Dr. Penfield made a strong plea for Federal Government aid to the universities of the country, as national institutions. He cited the exodus of our well-trained graduates to the United States as symptomatic of the poverty of opportunities for young scholars in our universities at a decent income. One of the greatest agencies for good in this country, the National Research Council, would be the natural body for the allocation of such help. Dr. Penfield also dealt with the requirements for the proposed new medical faculty in Vancouver.

A distinguished visitor to Canada has been Sir Henry Dale, the Nobel laureate in medicine. He gave the twelfth Hughlings Jackson Memorial Lecture of the Montreal Neurological Institute and later attended the annual meeting of the Canadian Physiological Association in Toronto.

Americans and Canadians have been reading a best-seller, "The Snake Pit", reminiscent of Charles Reade's "Hard Cash" almost one hundred years ago, on the distressing state of mental hospital care. The readers have now been provided with a bill of omissions from "The Snake Pit" survey, in the form of a lay article by Walter B. Pitkin, who shows that during the last sixty years there has been a twelvefold increase in mental diseases in the United States of America. One person in twenty will sooner or later be treated in a mental hospital there. Doctors in State mental hospitals care for an average of 240 patients each. Finally it is stated that to give even the care pictured in "The Snake Pit" to those needing it in the United States of America would cost three billion dollars, or twenty times the present expenditure.

Apropos of "spending to save" in mental disease, the Government of Saskatchewan has recently bought a former Royal Air Force station in a farming area and has transformed it into a mental institution for senile patients so that they will no longer occupy State hospital beds which may more properly be used for the active treatment of younger, possibly curable patients. The same Government will introduce on January 1, 1947, a compulsory system of hospital insurance covering public ward care, X rays, laboratory fees, drugs, dressings, operating room and physiotherapy. The cost will be $5.00 per person, with a maximum charge of $30.00 per family. This will greatly supplement the present public health coverage of the province, which costs participating municipalities thirty-three cents per person.

The current campaign in Canada for complete pasteurization of milk has brought to light the interesting fact that since the passage of the Province of Ontario's pasteurization law in 1938 not a single case of bovine tuberculosis from anywhere has been seen at the Sick Children's Hospital in Toronto.

Arthritis sufferers in Canada are keenly interested in the campaign now under way in the United States of America for $2,500,000 for a research centre to be built by the National Arthritis Research Foundation at Hot Springs, Arkansas.

Canada's hospital census now shows 58,407 public beds for acute cases, 3,484 for incurables; only 756 for convalescents; 11,057 for tuberculosis; 42,861 for mental disease; 4,522 in private nursing homes, and 21,808 in federal hospitals (veterans, military, marine and Indians).

Correspondence.

BACTERIAL ENDOCARDITIS.

SIR: In Dr. J. H. Halliday's excellent article on bacterial endocarditis, under the heading of "method of administration" of penicillin he mentions only the intravenous and intramuscular routes. Fully aware of the limitations to the deductions to be drawn from a "series of one" case, I feel that the results of the following case are worthy of mention. The patient, a female of twenty-six years, had a history of unexplained pyrexia, progressive heart involvement, and negative blood findings for some four months before the clinical picture of gross valvular lesions, and multiple emboli settled the diagnosis (concurred in by three other physicians). She was then given, during October and November, 1945, 300,000 units of penicillin daily for forty days (12,000,000 units). She was afebrile after twelve days, had a slight pyrexia on the nineteenth and twentieth days, after which she remained continuously afebrile. The transformation from toxic emaciation and gross cardiac failure to apparently normal health was dramatic. Since leaving hospital she has gone through an uncomplicated full-time first pregnancy with an uneventful confinement some twenty days ago. She carries out all her own housework unassisted and lives in a house with stairs. The point of this communication is that the penicillin was given by subcutaneous injection—100,000 units in one cubic centimetre of distilled water every eight hours, that is, 300,000 units daily. The subcutaneous method was suggested to me by the then current practice at an Australian general hospital. The small amount of local reaction was transitory and the subsequent nodule of induration at the site of injection passed away after a few days. The patient states that they have now been replaced by tiny dimples. The advantages of the simplicity of the subcutaneous route are obvious, and, of course, would reasonably make it the method of choice.

I can only suspect that those with more experience of the subcutaneous route have had less happy results than my one case. It would be interesting to hear more on the matter.

Yours, etc.,

201, Macquarie Street, Sydney, November 28, 1946.

R. D. DAVEY.

Obituary.

HARRIE LESLIE HUGO SCHÜTZE.

WE regret to announce the death of Dr. Harrie Leslie Hugo Schütze, which occurred at Berne, Switzerland, on August 9, 1946. Dr. Schütze graduated from the University of Melbourne in 1905 and received the doctorate of the University of Würzburg two years later. For over thirty years he had been a member of the bacteriological staff of the Lister Institute of Preventive Medicine in London.

BRYAN FOSTER.

WE regret to announce the death of Dr. Bryan Foster, which occurred on November 20, 1946, at Melbourne.

EWING GEORGE THOMSON.

WE regret to announce the death of Dr. Ewing George Thomson, which occurred on November 24, 1946, at Ascot, Queensland.

ALFRED JOHN GIBSON.

WE regret to announce the death of Dr. Alfred John Gibson, which occurred on November 25, 1946, at Bellevue Hill, New South Wales.

Nominations and Elections.

THE undermentioned has applied for election as a member of the New South Wales Branch of the British Medical Association:

Hollywood, Thomas Desmond, M.B., 1942 (Univ. Sydney), "Cloughmore", High Street, West Maitland.

Medical Appointments.

The following appointments have been made by the Board of Management, Royal Adelaide Hospital, Adelaide: Honorary Radiologist, Dr. J. S. Verco; Senior Honorary Assistant Radiologist, Dr. H. A. McCoy; Honorary Assistant Radiologists, Dr. C. Gurner, Dr. B. S. Hanson and Dr. B. C. Smeaton; Honorary Clinical Assistants to Radiological Section, Dr. P. W. Verco and Dr. R. de G. Burnard.

Notice.

C. E. FAWSITT PRIZE FUND.

IN order to perpetuate the memory of Professor C. E. Fawsitt, who retired from the chair of chemistry on August 31, 1946, after a long and distinguished service in the University of Sydney extending over a period of nearly forty years, it has been decided to establish a prize which will bear his name, and which will be awarded annually to a chemistry student of outstanding merit. The idea of inaugurating a fund for this purpose originated with the Sydney University Chemical Society, which appeals for subscriptions from science students past and present, and from others who may be interested in the prize because they have known Professor Fawsitt either as a teacher or as a friend. Should the fund reach the size hoped for, it may be possible to endow a scholarship which would be a more fitting reward for a brilliant chemistry student.

Subscriptions should be posted to the Honorary Secretary, Sydney University Chemical Society, Department of Chemistry, University of Sydney, and cheques *et cetera* made payable to the C. E. Fawsitt Prize Fund.

Diary for the Month.

DEC. 9.—Victorian Branch, B.M.A.: Executive Committee.
DEC. 10.—Tasmanian Branch, B.M.A.: Ordinary Meeting.
DEC. 10.—New South Wales Branch, B.M.A.: Executive and Finance Committee.
DEC. 11.—Victorian Branch, B.M.A.: Council Meeting.
DEC. 12.—New South Wales Branch, B.M.A.: Branch Meeting.
DEC. 12.—South Australian Branch, B.M.A.: Council Meeting.
DEC. 12.—Queensland Branch, B.M.A.: Annual Meeting.
DEC. 17.—New South Wales Branch, B.M.A.: Medical Politics Committee.
DEC. 17.—New South Wales Branch, B.M.A.: Ethics Committee.
DEC. 20.—Queensland Branch, B.M.A.: Council Meeting.

Medical Appointments: Important Notice.

MEDICAL PRACTITIONERS are requested not to apply for any appointment mentioned below without having first communicated with the Honorary Secretary of the Branch concerned, or with the Medical Secretary of the British Medical Association, Tavistock Square, London, W.C.1.

New South Wales Branch (Honorary Secretary, 135, Macquarie Street, Sydney): Australian Natives' Association; Ashfield and District United Friendly Societies' Dispensary; Balmain United Friendly Societies' Dispensary; Leichhardt and Petersham United Friendly Societies' Dispensary; Manchester Unity Medical and Dispensing Institute, Oxford Street, Sydney; North Sydney Friendly Societies' Dispensary Limited; People's Prudential Assurance Company Limited; Phœnix Mutual Provident Society.

Victorian Branch (Honorary Secretary, Medical Society Hall, East Melbourne): Associated Medical Services Limited; all Institutes or Medical Dispensaries; Australian Prudential Association, Proprietary, Limited; Federated Mutual Medical Benefit Society; Mutual National Provident Club; National Provident Association; Hospital or other appointments outside Victoria.

Queensland Branch (Honorary Secretary, B.M.A. House, 225, Wickham Terrace, Brisbane, B.17): Brisbane Associated Friendly Societies' Medical Institute; Bundaberg Medical Institute. Members accepting LODGE appointments and those desiring to accept appointments to any COUNTRY HOSPITAL or position outside Australia are advised, in their own interests, to submit a copy of their Agreement to the Council before signing.

South Australian Branch (Honorary Secretary, 178, North Terrace, Adelaide): All Lodge appointments in South Australia; all Contract Practice appointments in South Australia.

Western Australian Branch (Honorary Secretary, 205, Saint George's Terrace, Perth): Wiluna Hospital; all Contract Practice appointments in Western Australia. All government appointments with the exception of those of the Department of Public Health.

Editorial Notices.

MANUSCRIPTS forwarded to the office of this journal cannot under any circumstances be returned. Original articles forwarded for publication are understood to be offered to THE MEDICAL JOURNAL OF AUSTRALIA alone, unless the contrary be stated.

All communications should be addressed to the Editor, THE MEDICAL JOURNAL OF AUSTRALIA, The Printing House, Seamer Street, Glebe, New South Wales. (Telephones: MW 2651-2.)

Members and subscribers are requested to notify the Manager, THE MEDICAL JOURNAL OF AUSTRALIA, Seamer Street, Glebe, New South Wales, without delay, of any irregularity in the delivery of this journal. The management cannot accept any responsibility or recognize any claim arising out of non-receipt of journals unless such notification is received within one month.

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